# Neural temporal dynamics of negative emotional symptoms after iTBS in patients with stroke: a TMS-EEG study

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## Abstract

# Background

Stroke pathogenesis may be linked with aberrant neural network connections between brain regions and synapses plasticity. Furthermore, depression following a stroke does not arise from dysregulation in a singular brain region but rather from alterations across a “depression network”. While intermittent theta burst stimulation (iTBS) has been shown to alleviate depressive symptoms and modulate brain networks, but the effects of iTBS stimulation of the cerebellum on post-stroke negative emotional symptoms remain unexplored. Transcranial magnetic stimulation-electroencephalography (TMS-EEG) can offer insights into the dynamic mechanisms underlying iTBS treatment in stroke patients.

# Objectives

The study aims to investigate the temporal dynamics of the power spectrum and functional connectivity in post-stroke patients following iTBS over the cerebellum and to determine if iTBS targeting the cerebellum alters negative emotional symptoms in these patients.

# Methods

Twelve subacute stroke patients were enrolled, baseline data, along with clinical characteristics, were documented. Patients underwent iTBS treatment. Resting state EEG data were collected before and after in the initial and concluding iTBS sessions. Analyses were conducted on some indicators.

# Results

Under different periods’ iTBS intervention, in both the Alpha and Beta1 bands, there was a significant difference in the power spectrum and phase synchronization within regions of interest in stroke patients. A significant correlation was observed between phase synchronization and the self-rating depression scale score.

# Conclusions

In different periods, administering iTBS to target the cerebellum influenced the power spectrum, functional connectivity, and negative emotional symptoms in stroke patients.

## Introduction

Cerebrovascular accidents and depression contribute significantly to the global economic burden. Depression is one of the causes of disability worldwide [1], and stroke is marked third in the burden of disease [2]. Mood disorders, including post-stroke depression (PSD) and post-stroke anxiety (PSA), are mental complications of stroke [3], affecting approximately 30% of stroke survivors. Symptoms of post-stroke depression and anxiety arise from damage to the endocrine, nervous, and cardiovascular systems of stroke patients, negatively impacting their rehabilitation and quality of life. Post-stroke patients often experience aphasia and cognitive impairment, making it challenging for healthcare professionals and family members to comprehend their emotions and interests. Therefore, it brings great challenges to the diagnosis, evaluation, and treatment of mood disorder symptoms in stroke patients, and currently, limited literature is available to address this aspect [4]. Scholars have different opinions on the pathogenesis of PSD, which may be related to the general factors, lesion location, and disease-related factors [4]. Previous research had indicated that the prefrontal cortex, a crucial nerve center in the brain regulating thinking and behavior, was often damaged in patients with depression [5]. Wei et al. reported a significant association between right hemisphere stroke and the incidence of depression within 1–6 months of stroke [6]. Robinson's research showed a correlation between PSD and frontal lobe lesions [7]. In addition, the occurrence of PSD might be related to changes in the neurotransmitter system related to the frontal lobe/temporal lobe-basal ganglia-ventral brainstem. The basal ganglia has been shown to play an important role in the cortex and cortical circuits, including the frontal cortex, the frontal lobe motor network, and frontal-parietal-occipital nerve dysfunction in stroke which may be caused by basal ganglia disorders [8]. When the prefrontal cortex and basal ganglia experience infarction, the disruption in neurotransmitters related to emotional circuits and pathways can lead to depressive disorders.

The brain forms a highly complex network with interconnected regions, each governing specific tasks. This network ensures precise coordination across multiple spatiotemporal scales [9]. Connectomics provides a powerful analytical framework for localizing pathology, tracking disease transmission patterns, and predicting regions to be subsequently affected. Therefore, connectivity is at the core of understanding the pathology of neurological diseases. Clinical symptoms in patients may arise from disruptions in neural connectivity. Current research suggested that the destruction of brain functional connectivity was more important than the location of the lesion for PSD [10, 11]. Depressive symptoms do not arise from dysfunction in a single brain area; rather, they result from alterations in the "depression network," comprising connections among the neocortex, cingulate, limbic system, striatum, and thalamus [12]. Studies have suggested that symptoms of depressive disorders in stroke patients might be attributed to overactivation of the right parietal lobe, the posterior region of the temporal lobe, and central areas. It is well known that the frontal lobe can regulate emotion and cognition. Studies have shown that the activation of the frontoparietal cortex is reduced in the performance of working memory in elderly patients with depression, associated with symptoms such as anhedonia or blunted affect [13]. Changes in Alpha power observed in patients with major depressive disorder may reflect the activation decline in disease-associated regions such as the prefrontal cortex [14]. Some studies have employed functional magnetic resonance imaging (fMRI) to investigate the relationship between negative emotions, such as, anxiety and depression, and the resting state brain network in patients with subacute stroke. These

investigations have shown associations between patients with PSA and PSD and alterations in the resting state brain network. Additionally, the prefrontal cortex and cingulate cortex are related to the degree of depressive symptoms [15, 16]. Disturbances in functional brain networks provide a comprehensive model to elucidate the biological mechanisms underlying depression. In post-stroke patients, aberrant connectivity and pronounced neural plasticity associated with negative emotional symptoms might drive the pathogenesis of the disease. This may be particularly evident in brain regions where symptoms of "disconnect" manifest.

Due to continuous technological advancements, electroencephalography (EEG), a non-invasive brain stimulation technique, has become pivotal in brain research [17]. EEG signals come from post-synaptic excitatory or inhibitory potentials, which are generated by action potentials moving through the dendrites of pyramidal neurons in the outer layer of the cortex [18]. Compared with other neurophysiological techniques, EEG offers high temporal resolution and is characterized by its ease of operation, accessibility, and cost-effectiveness [18, 19]. EEG is increasingly utilized to assess human cognition, and serve as an objective biomarker for the early diagnosis and ongoing evaluation of cognitive impairments. EEG can detect changes in the power spectrum and network in patients with brain injuries. Resting-state EEG, recorded during quiet wakefulness, is valuable in clinical studies. It facilitates the extraction of biological markers that elucidate the mechanisms of cortical neuronal synchronization [20]. Additionally, two primary methods have been proposed for studying brain networks: measuring “effective connectivity” and “functional connectivity.” Functional connectivity is a potent tool for characterizing various brain functional states, such as those in healthy individuals or those with neurological or mental disorders, each exhibiting distinct features [21]. As a measure of neural synchrony, functional connectivity refers to the statistical interdependence between time-series data recorded from different brain regions and can be identified as two parameters: correlation and coherence. Connectivity analysis allows us to understand the functional systemic state and neural plasticity of complex brain networks. Doruk et al. found that the Delta, Theta, Alpha, and Beta interhemispheric coherence decreased in patients with depression, possibly because pathological conditions that affected the integrity of neural tissue could cause changes in the structure and function of the damaged area. Doruk et al. posited that observed the reduction in cerebral interhemispheric connectivity is indicative of post-stroke anatomical, adaptive and maladaptive changes in neural connections between damaged and undamaged cerebral hemispheres [22]. Studies have investigated the functional connectivity of amygdala subregions in patients with major depression, showing that the functional connectivity between the right central medial, lateral basal, and right middle frontal gyrus may be responsible for the neurobiological mechanism of anxiety-induced depression [23].

Transcranial magnetic stimulation (TMS) is widely used in evidence-based treatments for depression and post-stroke depression symptoms. Therefore, transcranial magnetic stimulation therapy has been studied extensively. TMS is a non-invasive brain stimulation technique that specifically modulates the human nervous system regarding to cognitive and behavioral functions. Repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS) targeting specific cortical regions can modulate neural circuits and improve symptoms and outcomes in patients with psychiatric disorders and abnormal behaviors, especially guided by resting-state and task-related neuroimaging measures [24].

iTBS induces plasticity of specific brain regions in patients with depression through accelerated, high-dose, functional connectivity-oriented targeted stimulation. iTBS has shown a measurable therapeutic impact on depression in certain cases. An animal model study has demonstrated effectiveness in inducing neural synaptic plasticity using high-frequency theta bursts stimulation protocols [25]. iTBS regulates a balance between the GABAergic and glutamatergic systems. However, the dysregulation of this system is a key feature of depression. Compared to sham stimulations in healthy individuals, the GABAergic to glutamatergic neurons ratio decreased, and effective connectivity of the right anterior insula, as well as the dorsolateral prefrontal lobe (DLPFC), increased after iTBS, which may reveal a possible mechanism of iTBS in the pathophysiology of depression [26, 27]. In patients with major depressive disorder, iTBS primarily modulates the anterior cingulate circuit, including the anterior cingulate cortex (ACC) and medial prefrontal cortex (PFC) (i.e., two theta-prominent brain regions). It has been demonstrated that frontal theta activity, recorded from the scalp, increases during cognitive tasks and is associated with enhanced ACC glucose uptake. This evidence can be used to predict better antidepressant efficacy [28, 29].

The combination of TMS with EEG (TMS-EEG) has garnered interest as a tool to record immediate and downstream cortical responses following magnetically targeted stimulation [30]. Studies using TMS-EEG have demonstrated that fronto-midline Theta power and Theta connectivity show good potential for predicting responses to rTMS treatment for depression [31]. A study of enhanced resting state EEG Gamma power and Theta-Gamma coupling (TGC) after high-frequency rTMS in the left dorsolateral prefrontal lobe of patients with depression suggested that resting state Gamma power and TGC may represent potential biomarkers of depression improvement associated with rTMS therapeutic efficacy [32]. TMS-EEG can reveal physiological activity in specific brain regions, and provides insights into the cross-sectional structure and functional connectivity of electrodes, and employ brief magnetic pulses to momentarily activate targeted cortical areas. At the same time, it captures neuronal responses through electrodes on the scalp [33], which allows us to gain a unique insight into cortical responses in stimulated regions and the wider cortical network. TMS-EEG offers a direct, objective, and non-invasive means to characterize various properties of the cerebral cortex, including excitatory and inhibitory responses, oscillatory patterns, and functional connections [24]. Therefore, TMS-EEG analysis provides a better understanding of neural network alterations and introduces a novel diagnostic and therapeutic approach for post-stroke negative emotional symptoms.

The cerebellum is small in size, but it contains more than 70% of the neurons in the brain and plays a key role in many brain functions and injuries, including sensory, motor, cognitive, and emotional processes. The cerebellum’s repetitive modular cortical structure suggests it plays a fundamental role in many aspects of brain function. It has been suggested that the cerebellum may play a fundamental role by regulating the timing necessary for temporal dynamics in information processing. Simple and complex spikes in the Purkinje cells of the cerebellar cortex regulate the temporal patterns related to the function of the inferior olivary nucleus [34]. However, few studies have explored the relationship between post-stroke negative emotional symptoms and brain networks following iTBS over the cerebellum. Therefore, our group conducted research using TMS-EEG to investigate the temporal dynamics between negative

emotional symptoms and brain networks in stroke patients who underwent iTBS over the cerebellum. Our research objectives are: (1) to examine the temporal dynamics in the power spectrum and functional connectivity of post-stroke patients following iTBS over the cerebellum and (2) to determine if iTBS over the cerebellum alters the negative emotional symptoms in these patients.

## Methods

# Participants

According to the inclusion and exclusion criteria, fifteen patients with stroke in the middle cerebral artery area were recruited at the Department of Rehabilitation Medicine in the Second Affiliated Hospital of Kunming Medical University from June 2022 to December 2022. Specially trained rehabilitation physicians and therapists conducted all procedures of patient recruitment. However, of the initial group, three patients were excluded: one due to poor cooperation and two because of substandard data quality identified during preprocessing. In total, twelve stroke patients met the criteria and provided informed consent. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (No: Shen-PJ-Ke-2022-22). This study was registered with the Chinese Clinical Trial Registry under the trial registration number [No. ChiCTR2200058553].

Inclusion criteria: 1) unilateral middle cerebral artery stroke diagnosed by CT or MRI; 2) age between 18 years old and 80 years; 3) stroke duration between 3 weeks and 6 months; 4) MMSE score above 11 points; 5) right-handed participants.

Exclusion criteria: 1) history of epilepsy or mental illness; 2) severe comorbidities; 3) presence of a pacemaker or intracranial metallic implants; 4) contraindications to TMS treatment; 5) non-compliance with the study protocol; 6) pregnancy; 7) take any psychiatric medications.

# Demographic and clinical characteristics of participants

All patients underwent clinical and neurological assessments at baseline (T0) and two weeks post-treatment (M0). Basic clinical information mainly included gender, age, ethnicity, education level, stroke type, duration of disease, brain damage area, and medical history. Neurological function scales mainly included National Institutes of Health Stroke Scale (NIHSS), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Working Memory (WM), Boston Naming (BN), Modified Barthel Index (MBI), Hamilton Depression Rating Scale (HAMDS), Hamilton Anxiety Scale (HAMA), Montgomery Depression Rating Scale (MADRS), and Depressive Symptom Self-Rating Scale (IDSSR).

# Study protocols

# Data collecting

Resting-state EEG data were obtained using a TMS-EEG system comprising a TMS instrument (model NS5000, manufactured in Wuhan, China) and an EEG device (model NSM2 by Biosemi, supplied by

Technocon, Qingdao, China) set up by a dedicated engineer and physician. A six-minute resting-stated EEG with closed eyes was used to analyze the changes in brain activities before and after the intervention of iTBS. All patients underwent conventional rehabilitation using an iTBS protocol with a figure-8 coil (model B9076, coil diameter 92 mm) once a day for 3–4 minutes, 5 times a week, for two weeks. The coil was tangent to the scalp, and the handle pointed upward. There were four conditions for each patient: 1) before the first iTBS intervention (T1), 2) after the first intervention (T2), 3) before the last intervention (M1), and 4) after the last intervention (M2). During EEG acquisition, the subjects were instructed to sit comfortably, keep their eyes closed, and remain quiet and awake. EEG signal acquisition was conducted using a 24-channel Biosemi system (FP1, FP2, F3, F4, F7, F8, Fz, T3, T4, T5, T6, A1, A2, C3, C4, Cz, P3, P4, Pz, O1, Oz, O2), model: CM-TK01-202455-E, provided by Qingdao Tylenox Company (including cable set), the amplifier, and the signal acquisition software. All channels were placed according to the 10–20 arrangement system. The ground electrode was placed between Fz and Cz, and the reference electrode was placed between Cz and Pz. The sampling rate was 1000 Hz, the bandpass filtering range was 0-100 Hz, and the impedance of all electrodes was below 5 KΩ during the experiments. The bilateral mastoid was served as the reference electrode.

# Data preprocessing

The raw EEG data were offline preprocessed using Matlab2020b (MathWorks, Inc., Natick, MA, USA) and the EEGLAB version 2020b toolbox (http://eeglab.org). Preprocessing steps included: channel selection, removal of redundant electrodes, down-sampling (from 1000Hz to 500Hz), bandpass filtering (0.1–40 Hz), notch filtering (48–52 Hz), segmentation (0–2 s), baseline correction, replacing bad electrodes, discarding defective segments, re-referencing to bilateral mastoids (A1/A2), employing independent component analysis (ICA) to eliminate artifacts (such as electro-ocular, electromyographic, and electrocardiographic components) and removing outliers. The schematic diagrams are shown in Fig. 1.

# Power spectrum

EEG rhythms included the Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), Beta1 (13–20 Hz), Beta2 (20–30 Hz) bands. The power spectrum under each frequency band was calculated using the STUDY toolbox.

# Functional connectivity

The Phase Lock Value (PLV), widely utilized in traditional EEG analyses mitigates interference from signal phase and amplitude components. The value range of PLV was 0 ~ 1. The average PLV was calculated in each frequency band.

# Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics 26.0 (IBM Corp.). The EEGLAB toolbox and CSD toolbox for MATLAB were used to compute power spectra and functional connectivity metrics (phase synchronization). Multiple comparisons of functional connectivity indicators in each frequency band were performed using the two-sample t-test in the Network-Based Statistics (NBS) toolkit. We

applied Bonferroni correction to the power spectrum under each frequency band, setting a significance level ($p < 0.05$). Comparisons with multiple groups were performed with one-way repeated measures ANOVA. Functional connectivity of the brain network was visualized using BrainNet Viewer 1.53 (Beijing Normal University, http://www.nitrc.org/projects/bnv/). Using Pearson correlation analysis, we calculated correlations between the power spectrum, functional connectivity, and neuropsychological scales, with corrections made using the False Discovery Rate (FDR).

## Results

# Basic clinical features

# Demographics

The study assessed 12 stroke patients pre- and post-treatment. The basic characteristics of the population are shown in Table 1. The mean age of the patients was 56.17 (7.19) years. The cohort comprised 9 males and 3 females; 5 had left brain damage while 7 had right brain damage; 10 experienced ischemic strokes, and 2 had hemorrhagic strokes. The detailed information on the stroke sites of the patients is shown in Table 2, where each patient is listed by a unique serial number. For most of the 12 patients, the primary affected areas were the basal ganglia, frontal lobe, temporal lobe, and parietal lobe.

Table 1
Demographic characteristic.

| | T0 (N = 12) | M0 (N = 12) |
|---|---|---|
| Age (years) | 56.17 (2.286) | 56.17 (2.286) |
| Sex (N, %) | | |
| Male | 9 (75.0) | 9 (75.0) |
| Female | 3 (25.0) | 3 (25.0) |
| Nation (N, %) | | |
| Han | 11 (91.7) | 11 (91.7) |
| Yi | 1 (8.3) | 1 (8.3) |
| Brain injury area (N, %) | | |
| Left | 5 (41.7) | 5 (41.7) |
| Right | 7 (58.3) | 7 (58.3) |
| Stroke classification (N, %) | | |
| Ischemia | 10 (83.3) | 10 (83.3) |
| Hemorrhage | 2 (16.7) | 2 (16.7) |
| Handedness (N, %) | | |
| Right | 12 (100) | 12 (100) |
| Education (N, %) | | |
| Primary | 4 (25.0) | 4 (25.0) |
| Junior | 3 (33.3) | 3 (33.3) |
| Senior | 2 (16.7) | 2 (16.7) |
| Bachelor | 3 (16.7) | 3 (16.7) |
| Medical history (N, %) | | |
| Hypertension | 8 (66.7) | 8 (66.7) |
| Diabetes | 2 (16.7) | 2 (16.7) |

T0: baseline; M0: two weeks post-iTBS treatment.

Table 2
Stroke sites detailed information.

| Number | Age | Sex | Stroke sites |
|---|---|---|---|
| 38 | 61 | Male | Basal ganglia |
| 61 | 63 | Male | Basal ganglia |
| 36 | 59 | Male | Basal ganglia |
| 59 | 56 | Female | Parietal lobe, Temporal lobe, Occipital lobe, Insular lobe |
| 1 | 36 | Male | Insular lobe, Occipital lobe, Basal ganglia |
| 15 | 62 | Female | Basal ganglia, Corona radiata, Peripheral white matter |
| 70 | 50 | Male | Corona radiata, Peripheral white matter, Frontal lobe, Parietal lobe |
| 55 | 51 | Male | Insular lobe, Basal ganglia |
| 67 | 59 | Male | Basal ganglia, Corona radiata |
| 73 | 56 | Male | Basal ganglia |
| 43 | 66 | Male | Parietal lobe, Temporal lobe, Frontal lobe |
| 76 | 55 | Female | Basal ganglia, Corona radiata |

Serial numbers were based on the collected patient data in order.

# Neurological function scores before and after treatment

After two weeks of iTBS treatment, the improvements in neurological deficits, as measured by NIHSS and MBI, were significantly greater than those observed pre-intervention ($p = .008$, $p = .003$); the symptoms of depression and anxiety, as measured by HAMDS, HAMA, and MADRS, showed significant improvement post-intervention ($p = .014$, $p = .004$, $p = .005$). For the cognition function, the MoCA score and the WM increased significantly post-intervention ($p = .006$, $p = .005$) (Table 3).

Table 3
Neurological score.

| Measures | T0 (N = 12) Mean (SD) | M0 (N = 12) Mean (SD) | *t* | *p* |
|---|---|---|---|---|
| NIHSS | 4.50 (3.680) | 3.42 (3.370) | 3.22 | 0.008*** |
| MMSE | 19.83 (8.244) | 21.92 (9.307) | -2.93 | 0.014*** |
| MoCA | 14.58 (7.786) | 17.25 (8.313) | -3.37 | 0.006*** |
| HMDS | 4.17 (3.306) | 3.25 (3.019) | 2.93 | 0.014*** |
| HAMA | 3.33 (1.923) | 2.08 (1.730) | 2.32 | 0.040*** |
| MADRS | 2.58 (1.730) | 1.92 (1.564) | 3.55 | 0.005*** |
| WM | 8.33 (2.570) | 9.25 (2.734) | -3.53 | 0.005*** |
| Barthel | 67.50 (23.404) | 76.67 (17.753) | -3.74 | 0.003*** |
| IDSSR | 11.58 (7.465) | 9.75 (7.521) | 1.56 | 0.146 |

Values are presented as mean (SD). *t* values were obtained using paired t-tests. ***: $p < 0.05$. SD: standard deviation; T0: baseline; M0: two weeks post-iTBS treatment; NIHSS: National Institutes of Health Stroke Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment Scale; HAMDS: Hamilton's Depression Scale; HAMA: Hamilton Anxiety Scale; MADRS: Montgomery Depression Scale; WM: Working Memory Scale; Barthel: Improved Barthel Index Rating Scale; IDSSR: Depression Symptom Scale; T0: baseline; M0: two weeks post-iTBS treatment.

# Power spectrum

# Frequency-specific power spectrum topographic map analysis

The Delta band power at T1 in the frontal and prefrontal regions exceeded that at T2, as depicted in Fig. 2 (A/B/C). The Theta band power in the right prefrontal and temporal lobes was notably higher at T1 than at T2. In the left frontal and temporal lobes, the Alpha band power was significantly reduced at T2 compared to T1. There was no statistical difference in the Beta1 and Beta2 bands power between T1 and T2.

After two weeks of treatment, the Delta band power in the frontal lobe, prefrontal cortex, and parietal lobe at M2 was significantly elevated compared to T2. The Theta band power, in the orbitofrontal cortex, prefrontal cortex, and temporal lobe was markedly higher at M2 than at T2. In the right frontal lobe, the Alpha band power at M2 was significantly elevated compared to T2. Beta1 band power in the right frontal

and temporal lobes was notably higher at M2 than at T2. Moreover, no statistical difference was observed in the Beta2 band power between T2 and M2, as illustrated in Fig. 2 (a/b/c/d). In addition, there was no significant difference in other periods for the power spectrum topographic map.

**Based on the topographic map, obtained the power spectrum differences of the regions of interest in different frequency bands**

Power in the Delta, Alpha, and Theta bands showed significant differences from T1 to T2 period, except for the left prefrontal lobe and right frontal lobe (FP1 and F8) ($p < 0.05$). Moreover, there were significant differences in these bands power from T2 to M2 period, except for the right prefrontal lobe and left frontal lobe (FP2 and F3) ($p < .05$). However, all bands power no significant differences between the M1 to M2 and T1 to M1 periods. The Beta1 band power in the right frontal lobe (F4 and F8) demonstrated a significant difference from the T2 to M2 period ($p < .05$). Across all periods, there was no significant difference in the Beta2 band power, as shown in Fig. 5 (A ~ F).

# Temporal trends and difference of power spectrum in the regions of interest

Figure 4 (A-F) illustrates the variability in the average power spectrum across distinct frequency bands at various time points. In regions including the left prefrontal cortex (FP1), frontal lobe (F3), right prefrontal cortex (FP2), and frontal lobes (F4/Fz/F8), there was a noticeable downward trend in the average power spectrum across all frequency bands from T1 to T2. The decline in the Delta, Theta, and Alpha frequency bands were more pronounced. After two weeks of iTBS treatment, there was an upward trend in the average power across all frequency bands from M1 to M2. However, the average power in the Beta1 and Beta2 bands remained consistent, with no discernible trend.

In addition, the left prefrontal lobe (FP1) in Beta2 band power showed differences among the four periods ($p = .039$). Differences were observed in the right prefrontal lobe (FP2) in Delta band power across the four periods ($p = 0.048$). The right frontal lobe (F4) showed significant differences in Delta, Theta, and Alpha bands power ($p = .003$, $p = .005$, $p = .022$). No significant differences in power spectrum values were observed in the remaining regions of interest in the four periods (Fig. 4 (a-f)).

# Functional connectivity analysis

Functional connectivity analysis revealed that the PLV in the Alpha and Beta1 bands at M2 was significantly elevated compared to T2. This change was predominantly observed in the orbitofrontal cortex, prefrontal cortex, frontal cortex, and temporal lobe ($p = .032$, $p = .040$) (Fig. 5). However, functional connectivity was not statistically significant in other time and frequency bands.

# Correlations between EEG and neurological scores

Given the notable change in phase synchrony (PLV) at M2 in the Alpha and Beta1 frequency bands, we further analyzed the correlation between PLV at M2 and IDSSR post-treatment (M0). In the Alpha band, there was a negative correlation between the phase synchrony of the left mastoid (A1) and the left frontal lobe (F3) with the M0-IDSSR score ($p$ = .000, r = − .853) (Fig. 6 (A)); the phase synchrony between the right parietal lobe (P4) and the right frontal lobe (F4) was negatively correlated with the M0-IDSSR scores ($p$ = .000, r = − .951) (Fig. 6 (B)). However, there was no statistically significant correlation between PLV and M0-IDSSR in the Beta1 band.

No significant difference correlation between the power spectrum in the Alpha and Beta1 bands for regions of the interest and M0-IDSSR.

## Discussion

This study investigated temporal dynamics in the power spectrum and functional connectivity through TMS-EEG at four-different time points: T1, T2, M1, and M2. We also analyzed the correlation between phase synchronization and neurological function scores. Our results showed that, firstly, the Alpha and Beta1 bands power of the FP1/Fz/F4/F8 electrodes the first post-iTBS treatment were significantly different from the last post-iTBS treatment. Secondly, the Delta, Theta, Alpha, Beta1, and Beta2 bands showed a downward trend of the power spectrum in the prefrontal cortex and the frontal cortex between T1 and T2. However, after two weeks of iTBS protocol, the power spectrum for the Delta, Theta, Alpha, Beta1, and Beta2 bands in the same regions showed an upward trend from M1 to M2. Moreover, significant differences were observed in the Alpha and Beta2 bands power for the prefrontal (FP2) and frontal (F4) lobes across the four periods. Thirdly, after two weeks of iTBS treatment, the phase synchronization of Alpha and Beta1 bands in the prefrontal and frontal cortex significantly increased compared with the first post-iTBS intervention. Fourth, we found a significant correlation between Alpha phase synchronization in the prefrontal and frontal cortex and M0-IDSSR.

# Analysis of abnormal power spectrum

Initially, we observed a decreasing trend in the Alpha band power in the prefrontal cortex and the frontal cortices between T1 and T2 (Fig. 2, and Fig. 4). A TMS-EEG study of electroconvulsive therapy (ECT) for major depressive disorder (MDD) showed a decrease in the Alpha band power after treatment compared with that before treatment, suggesting that the reduction of prefrontal Alpha power represented MDD-related patients with better outcomes. This change might be indicative of modulations in the Alpha rhythm oscillatory activity, which has been associated with post-stroke plasticity and alterations in neural circuits post-TMS intervention [35]. Previous studies have shown distinct neuro-modulatory patterns in the prefrontal cortex compared to the motor cortex following rTMS intervention. For example, TBS directed the responsiveness of the prefrontal cortex [29, 36], indicating that different stimulus intensity or pattern parameters settings could have varied impacts on diverse cortical targets. The stimulus frequency would affect the brain's oscillations, which were made up of complicated linear sinusoidal oscillations and nonlinear amplitude-modulated signals. The discrepancies between our findings and prior research

could be attributed to the variations in analytical techniques and the inherent heterogeneity of depression [28]. In addition, the Alpha band power in the prefrontal cortex and frontal cortex was altered after two weeks of iTBS treatment compared with before the intervention (Fig. 3, and Fig. 4). Related studies have shown that the increased power of the Alpha band in the prefrontal cortex was correlated with clinical and cognitive improvements [37]. Long-lasting Alpha power enhancement was partially associated with the antidepressant [38]. Similarly, one TMS-EEG study demonstrated that a positive correlation between the left frontal Alpha power and depressive symptoms. For example, patients with major depression had increased Alpha oscillatory power. Additionally, our findings contradicted the results of a prior study [39], which displayed that a drop in Alpha power was related to a beneficial response to antidepressant therapies. The two experiments' disparate findings may be attributed to target selection for therapeutic intervention or to the diurnal fluctuations of alterations in the synaptic plasticity generated by Alpha oscillations. Overall, adjustments in the Alpha power were closely associated with emotional alterations.

The Beta1 band in the prefrontal and frontal lobes exhibited significant improvement and changes at T2 and M2 (Fig. 2, Fig. 3, and Fig. 4). Furthermore, the change in Beta2 band power within the frontal cortex across four periods (Fig. 4), may indicate a reflecting the therapeutic response to iTBS. Long-term paroxetine therapy was linked to an increase in Beta1 power in patients with major depression, according to post-medication EEG research, which suggested that Beta1 power was regulated by mood changes [40]. rTMS administered at 1 Hz over the right dorsolateral prefrontal lobe in depressed patients resulted in a marked increase in Beta oscillation [41]. An earlier investigation revealed that 1Hz-rTMS over the right DLPFC for treating depression led to a notable increase in Beta power. This observation partially clarified the therapeutic mechanism of 1Hz-rTMS over the right DLPFC [42]. However, Noda et al. observed that 20Hz-rTMS applied over the left frontal cortex in depressed patients significantly amplified Gamma band power, and this increase correlated with diminished depressive symptoms [32]. The increased power in the Beta and Gamma frequency bands may indicate a potential neuro-modulatory mechanism of rTMS intervention for depression, regardless of whether the target was left or right DLPFC [42].

Additionally, the Delta and Theta bands power in the prefrontal and frontal lobes exhibited significant improvement and changes at different times (Fig. 2, Fig. 3, and Fig. 4), suggesting that iTBS targeting the cerebellum may enhance slow-wave power in patients exhibiting post-stroke negative emotional symptoms. One study proposed that iTBS could modify the Gamma band power and functional connectivity in patients experiencing both self-compassionate and negative emotions. This research also documented a decline in Theta band power in patients with self-compassionate emotions prior to iTBS, with a subsequent rise post-intervention. This may be related to the social environment where the patients were living [43]. Iznak et al. examined changes in resting-state EEG after depression therapy. They discovered that amelioration in depressive symptoms correlated with augmented Delta and Theta power, predominantly in the frontal, central, and temporal areas of the right hemisphere [44]. Furthermore, the findings of their study were consistent with the present study, suggesting that increased prefrontal Delta and Theta power might indicate better working memory, attention, and mood.

# Analysis of phase synchronization and correlation

The present study observed an increased phase synchronization index in the Alpha band between the prefrontal and frontal lobes post-iTBS treatment in stroke patients (Fig. 5 (A)). Additionally, a correlation was identified between this enhanced phase synchrony and the M0-IDSSR (Fig. 6). Sun et al. suggested that stroke patients exhibited fewer functional connections in the left and right hemispheres of the brain compared to healthy individuals, and functional connectivity in the parieto-occipital and frontal lobes decreased as the severity of PSD worsened [45]. Phase synchrony, an EEG functional connectivity index, was used in one study to predict the severity of depression. The study showed a negative correlation between the level of depression and both Alpha phase synchrony and the graph theory index [46]. Patients with bipolar disorder (BD) also exhibited lower mean synchronization in the Alpha band and abnormalities in functional brain connections. Another research revealed that thalamic generators of the Alpha oscillation had a strong impact on cortical Alpha rhythms [28]. Major depression was postulated to represent disrupted thalamocortical connections, which had a negative impact on the Alpha oscillation of the thalamus. Abnormalities of the Alpha oscillation in the cerebral cortex, including the anterior cingulate cortex and the prefrontal cortex, might be modulated after rTMS over the prefrontal lobe by providing top-down control of thalamic and thalamocortical cortical Alpha oscillations and restoring functional links with the anterior thalamus. Additionally, the reduction in functional connectivity between the frontal and parietal lobes in patients with PSD resulted in an imbalance of the Alpha band power and the cerebral hemisphere, which might be associated with emotional control in post-stroke patients [22]. These findings suggested that a decrease in negative emotional symptoms correlates with increased functional connectivity in the Alpha band, aligning with our observations.

Our study also observed an increase of the Beta1 phase synchronization in the prefrontal lobe in stroke patients after iTBS treatment (Fig. 5(B)). However, there was no association between phase synchrony and M0-IDSSR. The alteration of functional connectivity in the Beta band in the inferior frontal lobe was observed in individuals with major depression prior to and following TMS treatment [47]. The increase in functional connectivity in the Beta band, which was a sign of plasticity potential, suggested a shift in the plasticity of the brain network and negative emotional symptoms for stroke [22].

In short, iTBS over the cerebellum could dramatically improve the Alpha and Beta1 bands phase synchronization, which might elucidate the therapeutic mechanism underlying the amelioration of negative emotional symptoms of post-stroke.

# Limitations

Limited studies have explored the variations in power spectra and functional connectivity before and after iTBS treatment. Our investigation revealed a decrease in band power following the initial iTBS intervention, whereas subsequent iTBS interventions led to an increase across all bands. There were two limitations in this study. First, our sample size was limited, with only 12 patients included. This might impact the universality of our data. Second, our pooled data lacked a healthy control group for comparison. Incorporating a control group would have strengthened our evidence.

# Conclusion

This study identified significant variations in the power of Alpha and Beta bands in the prefrontal and frontal lobes post-iTBS treatment. Concurrently, we observed enhanced functional connectivity and increased phase synchronization in stroke patients. This study highlights the temporal dynamics between negative emotional symptoms in stroke patients and iTBS stimulation. Understanding these dynamics can guide more effective diagnostic and treatment protocols, potentially alleviating the negative emotional symptoms of these patients.

# Declarations

Consent to patient

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

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Competing interests:

The authors have no competing interests to declare that are relevant to the content of this article.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (No: Shen-PJ-Ke-2022-22).

Clinical Trial Registration

This study was registered with the Chinese Clinical Trial Registry under the trial registration number [No. ChiCTR2200058553]. date of registration is 2022.

Author’s Contribution Statement:

Conceptualization, Methodology, Software by Xue Yang. Methodology, Investigation, Formal analysis, Validation, Visualization, Roles/Writing - original draft, and Writing - review & editing by Qian Liu. Project administration, Data curation, Investigation by Hongmei Zhang. Investigation, Project administration by Yihuan Lu. Methodology, Data curation by Xueting Chen. Methodology by Tianling Wang.

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# Figures

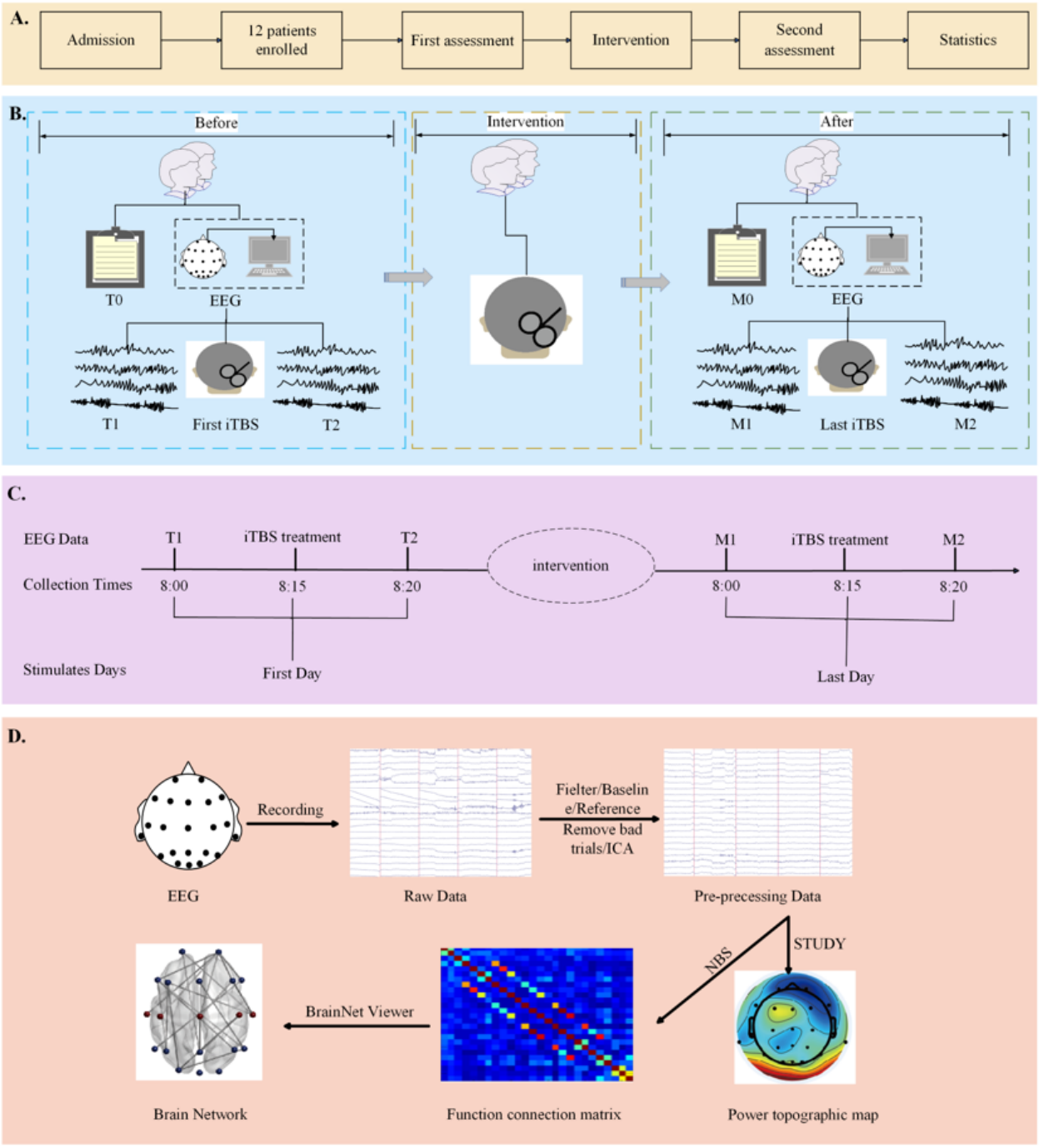


**Fig. 1** The schematic diagrams. A. Technology roadmap. B. The flowcharting of data collected. C. The timer shaft of iTBS treatment and EEG collected. D. The construction of brain network. T0: baseline. M0: two weeks post-iTBS treatment. T1: the first pre-iTBS treatment. T2: the first post-iTBS treatment. M1: the last pre-iTBS treatment. M2: the last post-iTBS treatment. iTBS: intermittent Theta Burst Stimulation

## Figure 1

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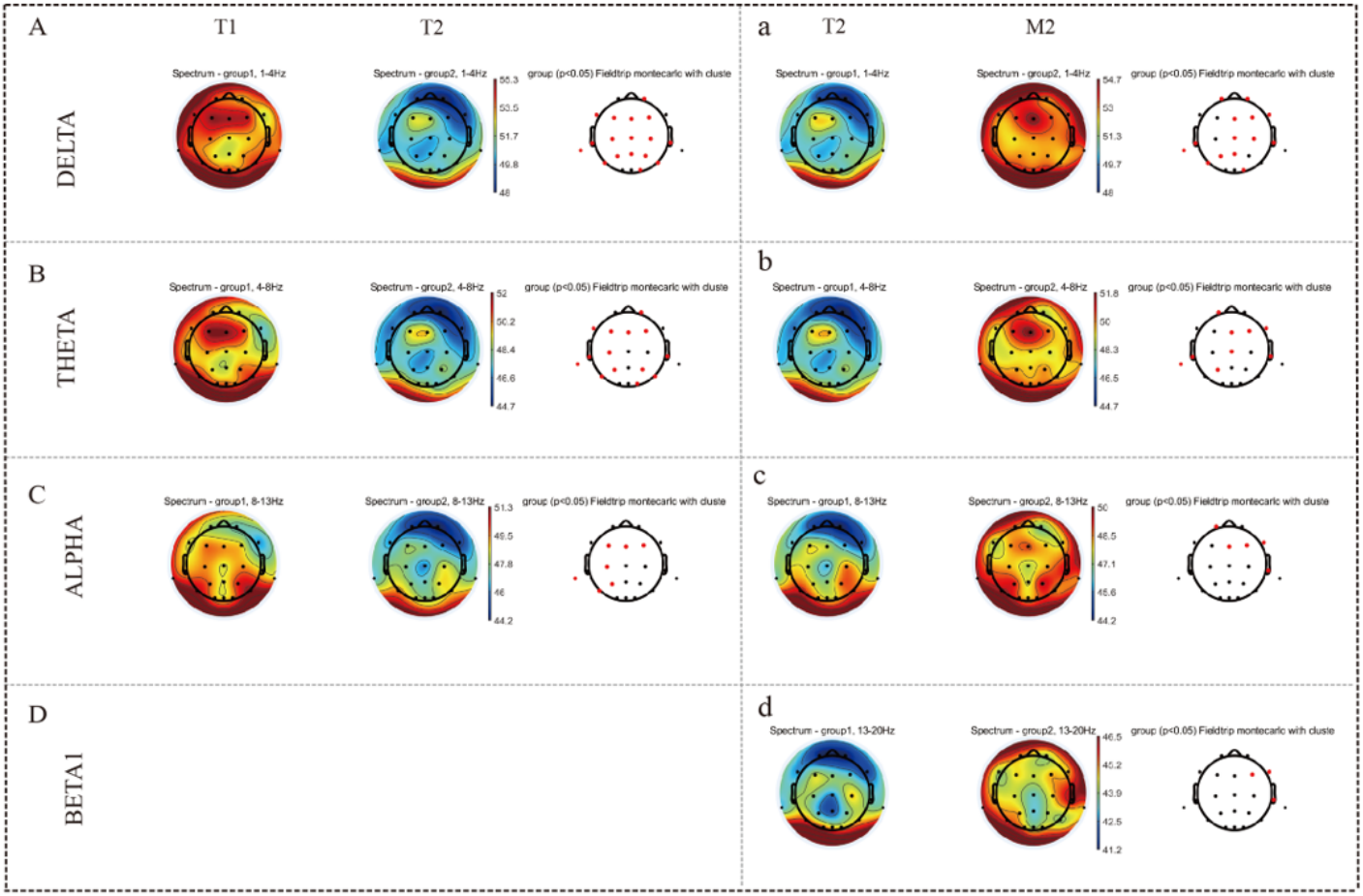


**Fig. 2** Power spectrum topography before and after iTBS treatment. A/B/C: Power spectrum topography in the Delta/Theta/Alpha band before (T1) and after (T2) the first iTBS treatment. a/b/c/d: Power spectrum topography in the Delta/Theta/Alpha/Beta1 band after the first iTBS treatment (T2) and after the last iTBS treatment (M2). T1 and T2: the first pre- and post-iTBS treatment. M1 and M2: the last pre- and post-iTBS treatment. Delta: 1~4Hz. Theta: 4~8Hz. Alpha: 8~13Hz. Beta1: 13~20Hz. The red dots: statistically significant for different brain regions in different frequency bands ($p < 0.05$)

## Figure 2

See image above for figure legend.

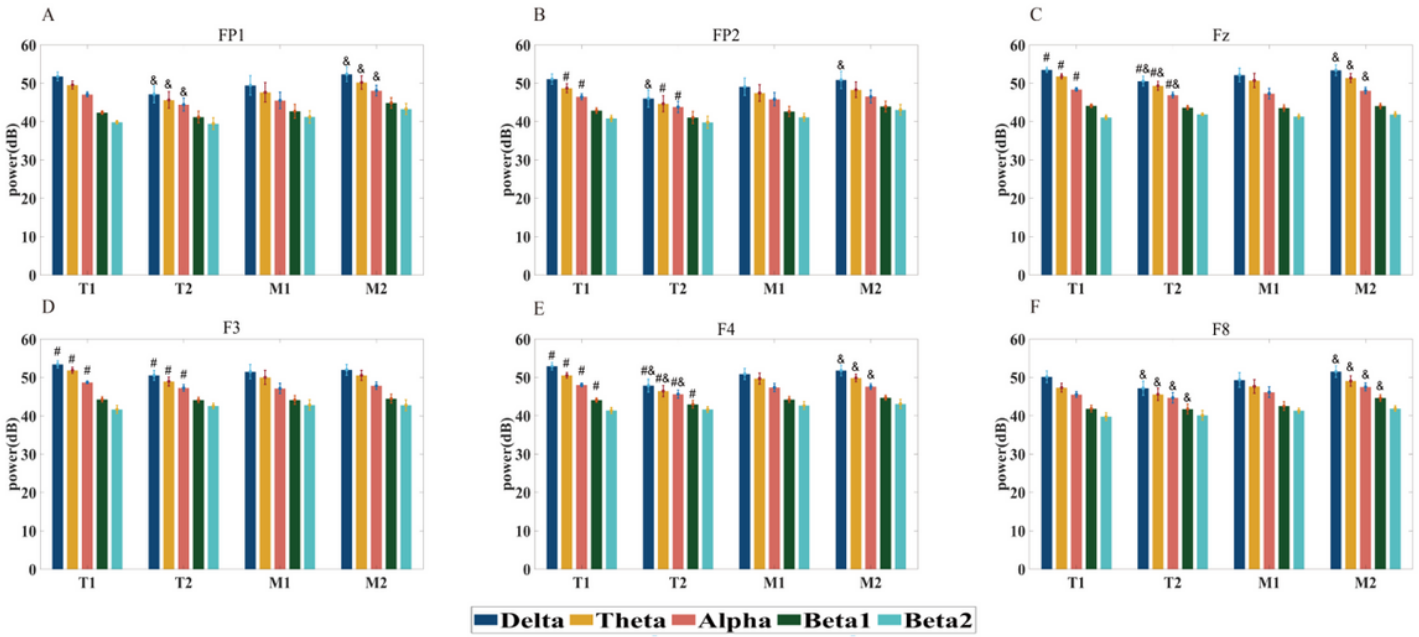


**Fig. 3** The power spectrum differences of the regions of interest in different frequency bands. A: the prefrontal lobe FP1. B: the prefrontal lobe FP2. C: the frontal lobe Fz. D: the frontal lobe F3. E: the frontal lobe F4. F: the frontal lobe F8. T1: the first pre-iTBS treatment. T2: the first post-iTBS treatment. M1: the last pre-iTBS treatment. M2: the last post-iTBS treatment. Delta: 1-4Hz. Theta: 4-8Hz. Alpha: 8-13Hz. Beta1: 13-20Hz. "#": significant differences between T2 and T1 in each frequency band ($p < 0.05$). "&": significant differences between T2 and M2 in each frequency band ($p < 0.05$)

## Figure 3

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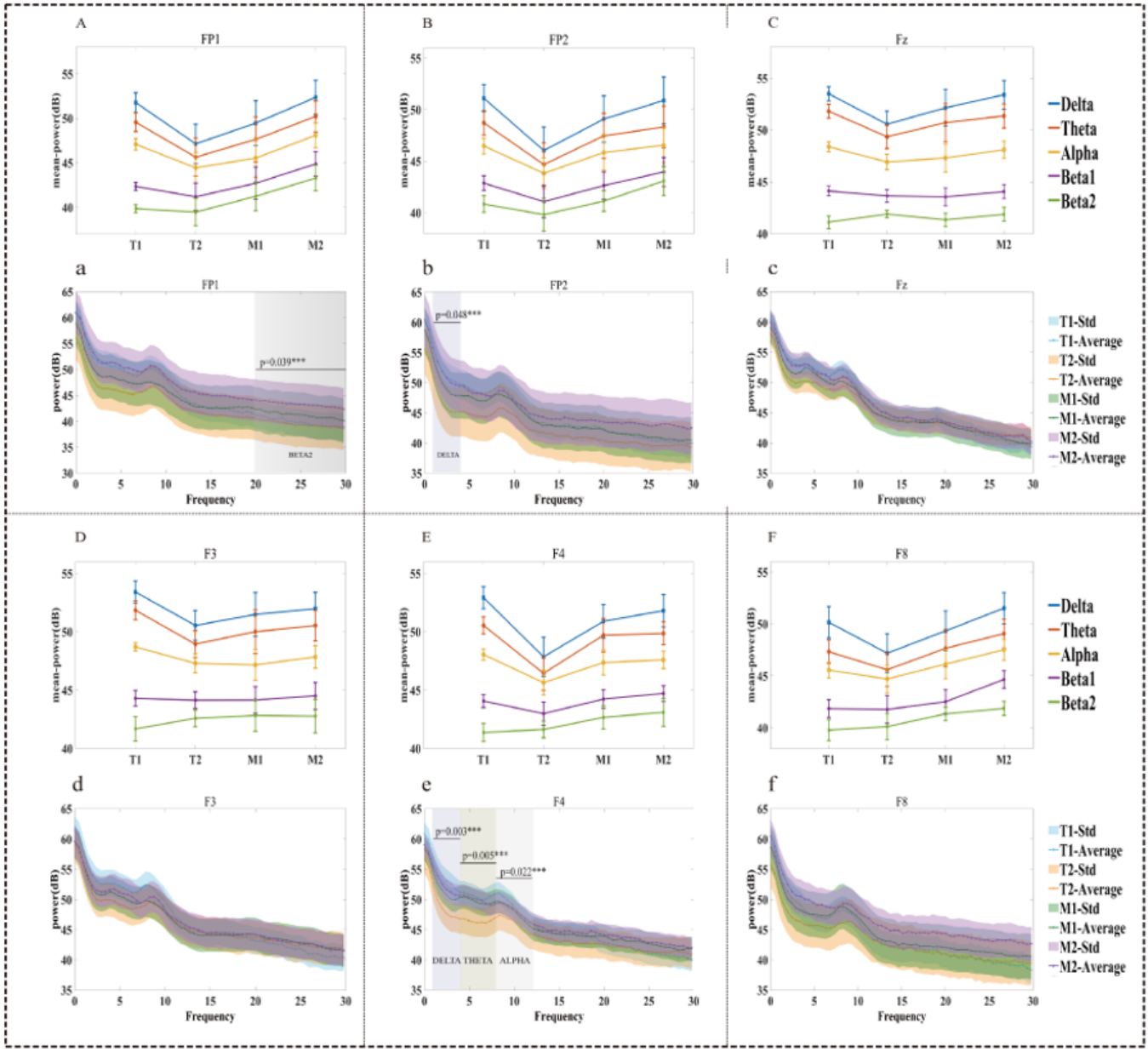


**Fig. 4** Temporal trends and differences in power spectrum of the regions of interest. A/a: the left prefrontal lobe FP1. B/b: the right prefrontal FP2. C/c: the left frontal lobe Fz. D/d: the right frontal lobe F3. E/e: the frontal lobe F4. F/f : the right frontal lobe F8. T1 and T2: the first pre- and post-iTBS treatment. M1 and M2: the last pre- and post-iTBS treatment. T1 and T2-Std: standard deviation of the power spectrum the first pre- and post-iTBS treatment. T1 and T2-Average: the mean of the power spectrum the first pre- and post-iTBS treatment. M1 and M2-Std: standard deviation of the power spectrum the last pre- and post-iTBS treatment. M1 and M2-Average: the mean of the power spectrum the last pre- and post-iTBS treatment. Delta: 1~4Hz. Theta: 4~8Hz. Alpha: 8~13Hz. Beta1: 13~20Hz. ***: $p$ <0.05. power(dB): power spectral density. Frequency: frequency

## Figure 4

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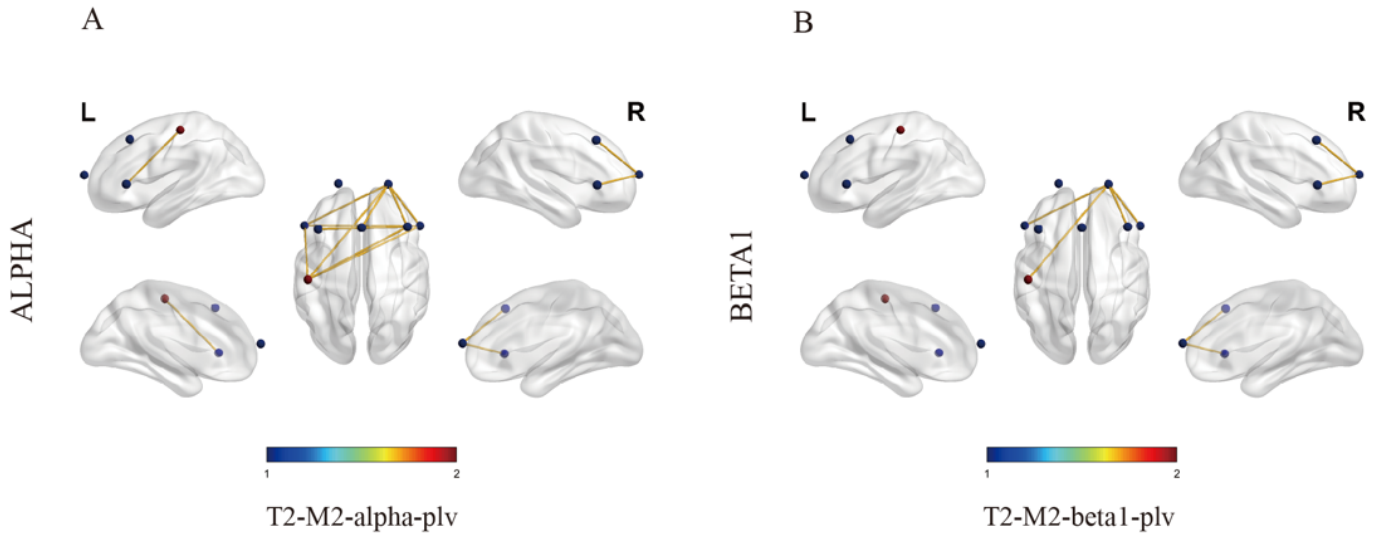


**Fig. 5** Functional connectivity the first post-iTBS treatment (T2) and the last post-iTBS treatment (M2). A/T2-M2-alpha-plv: phase synchronization in the Alpha (8~13 Hz) frequency band the first and last post -iTBS treatment. B/T2-M2-beta1-plv: phase synchronization in the Beta1 band (13~20Hz) the first and last post-iTBS treatment. L: left side of brain. R: right side of brain. Red and blue dots indicate brain regions in the frontal and prefrontal lobes. The yellow lines represent the functional connectivity density between brain regions

## Figure 5

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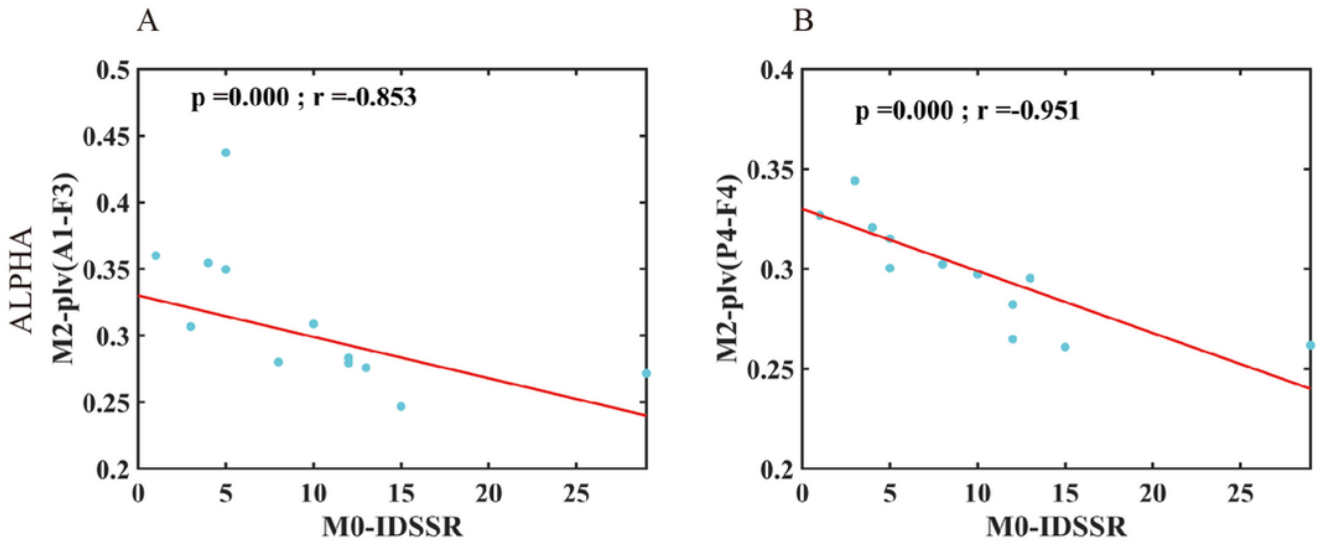


**Fig. 6** Correlation between PLV and IDSSR under different lobes in the Alpha band. A: correlation of A1 and F3 lobes at the last post-iTBS treatment PLV. B: correlation of P4 and F4 lobes at the last post-iTBS treatment PLV. M2: the last post-iTBS treatment. PLV: Phase Synchronization. M0-IDSSR: Depression Self-rating scale post-iTBS treatment. F3: left frontal lobe. F4: right frontal lobe. A1: left mastoid lobe. P4: right parietal lobe

## Figure 6

See image above for figure legend.