

Intermittent Theta Burst Stimulation of the Contralesional Hemisphere for Post-Stroke Visuospatial Neglect: An EEG and ERP-Based Randomized Controlled Trial

Yichen Zhang

Xuan Wu Hospital of the Capital Medical University

wanying Zhao

Xuan Wu Hospital of the Capital Medical University

weiqun Song

Xuan Wu Hospital of the Capital Medical University

huanxin Xie

Beijing Rehabilitation Hospital of Capital Medical University

Lei Cao

Xuan Wu Hospital of the Capital Medical University

Linlin Ye

yelinlin_xw@163.com

Xuan Wu Hospital of the Capital Medical University

Research Article

Keywords: Stroke, Visuospatial neglect, rsEEG, ERP, TMS

Posted Date: May 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9405668/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

This study aimed to investigate the clinical efficacy and underlying electrophysiological mechanisms of intermittent theta burst stimulation (iTBS) in treating post-stroke visuospatial neglect (VSN). By integrating high-temporal-resolution EEG/ERP techniques with clinical behavioral assessments, we sought to provide a multidimensional and objective scientific basis for developing precise, individualized neuromodulation protocols.

Methods

Thirty-nine patients with VSN in the subacute phase following a right-hemispheric stroke were enrolled and randomly assigned to either an iTBS group ($n = 20$) or a sham stimulation group ($n = 19$). The iTBS group received active stimulation over the dorsolateral prefrontal cortex (DLPFC) of the unaffected hemisphere (twice daily, 5 days per week, for a total of 20 sessions). The sham group received identical parameters but with the coil tilted perpendicular to the scalp. Both groups underwent conventional rehabilitation therapy. Clinical pen-and-paper tests, resting-state EEG, and task-related ERPs were evaluated before and after the intervention.

Results

Excitatory iTBS applied to the unaffected DLPFC significantly ameliorated neglect symptoms in patients with subacute post-stroke VSN. Neurophysiologically, the iTBS group exhibited a significant increase in alpha-band spectral power in the right parieto-occipital region, a marked decrease in the delta-alpha ratio (DAR), enhanced interhemispheric functional connectivity, and an increased P300 amplitude in the unaffected hemisphere.

Conclusion

iTBS effectively alleviates VSN symptoms by enhancing alpha-band neural oscillations and restoring interhemispheric functional connectivity. Furthermore, resting-state EEG and task-related ERPs serve as robust and reliable biomarkers for evaluating the efficacy of neuromodulatory interventions in visuospatial neglect.

1. Introduction

Visuospatial neglect (VSN) is a prevalent cognitive impairment following stroke, characterized by a patient's inability to respond, or a delayed response, to stimuli presented in the hemispace contralateral to the brain lesion [1]. This condition profoundly impacts the rehabilitation trajectory and quality of life of

stroke survivors. Although patients with VSN experience some degree of spontaneous neurological recovery within the first 12 weeks post-onset, approximately 40% continue to exhibit persistent symptoms one year later [2, 3]. Consequently, the early implementation of effective rehabilitation interventions is crucial for accelerating functional recovery and facilitating patients' successful reintegration into society.

In recent years, non-invasive central neuromodulation techniques, particularly transcranial magnetic stimulation (TMS), have demonstrated tremendous potential in VSN rehabilitation [4]. Theta Burst Stimulation (TBS), an optimized TMS paradigm, can induce rapid and enduring alterations in cortical excitability utilizing lower stimulation intensities and shorter administration durations (e.g., intermittent TBS [iTBS] increases, whereas continuous TBS [cTBS] decreases cortical excitability). Numerous studies have corroborated that TBS interventions can effectively ameliorate clinical symptoms in patients with post-stroke VSN.

Nevertheless, significant limitations persist in current evaluations of TBS efficacy and investigations into its underlying mechanisms for treating VSN [5, 6]. First, the majority of studies rely predominantly on traditional paper assessments. Such behavioral measures are not only susceptible to "learning effects," but also struggle to capture genuine improvements in activities of daily living. Furthermore, they fall short of elucidating the neurophysiological mechanisms driving the long-term behavioral modifications induced by TMS. Second, although neuroimaging techniques like diffusion tensor imaging (DTI) and resting-state functional MRI (fMRI) have confirmed that TBS alters functional and structural connectivity in local and remote brain regions [7, 8], these modalities lack the temporal resolution required to directly capture the transient, millisecond-level cortical dynamics inherent in complex attentional processes.

Electroencephalography (EEG) and event-related potentials (ERPs) offer exceptionally high temporal resolution, enabling the precise tracking of transient changes within cortical attention networks. Current research indicates that resting-state EEG spectral power and interhemispheric functional connectivity are highly sensitive to TBS and can reliably predict therapeutic responsiveness [9, 10]. Additionally, ERP components, such as the P300, have been proven to objectively reflect alterations in cognitive function following TMS interventions. Therefore, by integrating high-temporal-resolution EEG/ERP techniques with clinical behavioral assessments, this study aims to multidimensionally and objectively investigate the clinical efficacy and underlying electrophysiological modulation mechanisms of TBS in treating post-stroke VSN. Ultimately, this research seeks to provide a robust scientific foundation for developing more precise, individualized neuromodulation protocols in clinical practice.

2. Methods

2.1 Participants

Patients with post-stroke visuospatial neglect (VSN) in the subacute phase following a right hemispheric stroke were enrolled in this study. Participants were recruited from the Department of Rehabilitation

Medicine at Xuanwu Hospital, Capital Medical University, between March 2023 and December 2023. The presence of VSN was confirmed via standardized scale assessments. Eligible participants were randomly allocated into either the iTBS group or the sham-stimulation group. The randomization was conducted by two independent researchers who were not involved in the study using a computer random sequence generator. Allocation was concealed using sequentially numbered, opaque, sealed envelopes prior to making the incision. Both the participants and the outcome assessors were blinded to the group assignment. The details of group allocation were accessible only to the unblinded TMS therapist, who performed the stimulation but did not participate in any subsequent data collection or analysis. All participants were fully informed about the study procedures and provided written informed consent. The study protocol was reviewed and approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University.

(1) Inclusion criteria for patients with right hemispheric stroke were as follows:

- ☒ Diagnosis of stroke meeting the criteria outlined in the *Chinese Guidelines for Diagnosis and Treatment of Intracerebral Hemorrhage (2019)* or the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke (2018)*, confirmed by cranial CT or MRI as a first-ever stroke, with the lesion restricted to the right hemisphere;
- ☒ In the early subacute phase of stroke, defined as 7 days to 3 months post-onset [56];
- ☒ Aged between 18 and 80 years;
- ☒ Capable of completing resting-state EEG and event-related potential (ERP) data acquisition;
- ☒ Right-handedness;
- ☒ Provision of informed consent by the patients and their families.

(2) Exclusion criteria for patients with right hemispheric stroke were as follows:

- ☒ Neuroimaging evidence of multiple strokes or other brain injuries, or concomitant neurological or psychiatric disorders;
- ☒ Presence of severe complications or medical instability, aphasia, impaired consciousness, or the inability to maintain wakefulness and cooperate with clinical examinations;
- ☒ Severe cognitive impairment, defined as a Mini-Mental State Examination (MMSE) score < 17;
- ☒ Severe visual field defects;
- ☒ Recent use of medications known to affect EEG activity, such as tricyclic antidepressants or sedatives;
- ☒ History of epilepsy or active seizures;

☒ Presence of metallic implants in the head (e.g., cochlear implants, intracranial arterial stents, intracranial vascular coils, ventriculoperitoneal shunts, deep brain stimulators) or implanted cardiac pacemakers/infusion pumps.

2.2 Clinical and Behavioral Assessments

(1) Basic Clinical Data and Functional Assessments

Baseline clinical data for all stroke patients were recorded, including age, sex, time since onset, and lesion location. All patients underwent comprehensive evaluations of their activities of daily living (ADLs), motor function, and balance.

☒ Barthel Index (BI): The Barthel Index (BI) was utilized to evaluate the patients' basic self-care abilities in daily living.

☒ Fugl-Meyer Assessment (FMA): The Fugl-Meyer Assessment (FMA) was employed to evaluate the level of motor control in the patients' affected upper and lower extremities.

☒ Berg Balance Scale (BBS): The Berg Balance Scale (BBS) was used to assess the patients' dynamic and static balance capabilities, as well as their risk of falling.

(2) Visuospatial Neglect Scale Assessments

All participants were assessed in a quiet room. During testing, the test sheet was placed directly in front of the patient, ensuring that the midline of the paper perfectly aligned with the patient's body midsagittal plane. The severity of VSN was evaluated using the following four classic standardized scales:

☒ Line Bisection Test (LBT)

The test sheet contains five horizontal lines of varying lengths (80-160mm). Participants are required to mark the midpoint of each line. The distance by which the marked point deviates from the true midpoint is measured and converted into a percentage of the true half-length. A rightward deviation is recorded as a positive value, whereas a leftward deviation is negative. The average deviation across the five lines constitutes the Line Bisection Error (LBE). An average LBE $\geq 12\%$ is considered a positive result for VSN.

☒ Line Cancellation Test (LCT)

Thirty short lines are evenly distributed on the test sheet (15 on each side). Participants are instructed to cross out all the lines. The Omission Rate of Lines (ORL) is calculated as: $ORL = (\text{number of omitted lines}) / 30$. The test is considered positive if ≥ 3 lines are omitted (i.e., $ORL \geq 0.1$).

☒ Clock Drawing Test (CDT)

The test presents a circular clock face, with hands set to 1:35. The patient is instructed to copy the drawing onto the paper. The patient is considered to have left VSN if they omit the left half of the clock

face, omit the numbers on the left side, or if the numbers are drawn shifted to the right.

✶ Star Cancellation Test (SCT)

The test sheet features 56 target small stars (27 on each side, 2 in the center) randomly interspersed among distractor items, such as large stars and letters. Participants are required to cross out all target small stars. The Omission Rate of Stars (ORS) is calculated as: $ORS = (\text{number of omitted small stars}) / 56$. The test is considered positive if ≥ 5 target small stars are omitted.

Participants who tested positive for left VSN in any two of the aforementioned tests were assigned to the VSN group. Participants were assigned to the non-VSN group only if they yielded negative results across all four tests.

2.3 Resting-State EEG Acquisition and Analysis

Participants were seated comfortably in a quiet, electromagnetically shielded room. They were instructed to remain awake, relaxed, and with their eyes closed, while minimizing head movements and swallowing to reduce electromyographic (EMG) interference. A 64-channel Neuroscan system (Compumedics USA, Ltd.) was utilized to record 5 minutes of resting-state EEG signals in accordance with the international 10–20 system. During online recording, the tip of the nose served as the reference electrode, and the ground electrode was placed between FPz and Fz. The sampling rate was set at 1000 Hz, the bandpass filter at 0.05–100 Hz, and all electrode impedances were maintained at ≤ 10 k Ω .

(1) Preprocessing

Offline preprocessing of the EEG data was performed using the open-source toolbox EEGLAB (v13.0) implemented in MATLAB 2013b. The specific pipeline was as follows: ✶ Extraneous channels were removed, and channel locations were mapped; ✶ Filtering: A 0.1–40 Hz FIR filter was applied to the EEG data, followed by a 49–52 Hz notch filter to eliminate power-line interference; ✶ Segmentation: Data were segmented into 2-second epochs with no overlap; ✶ Artifact rejection and interpolation: Data underwent visual inspection. Electrodes with highly unstable signals were replaced using spherical interpolation. Epochs contaminated by artifacts such as gross head movements or swallowing were manually discarded; ✶ Re-referencing: The EEG data were re-referenced to the whole-brain average reference; ✶ Independent Component Analysis (ICA) was applied to identify and remove components associated with ocular artifacts (e.g., blinks and eye movements); ✶ Epochs in which the amplitude of any electrode exceeded $\pm 100\mu\text{V}$ were automatically rejected.

A Fast Fourier Transform (FFT) was utilized to calculate the power spectral density (PSD, expressed in $\mu\text{V}^2/\text{Hz}$) for each electrode within each epoch across the Hz range. Four neural oscillation frequency bands were defined: delta(1-4Hz)✶theta(4-8Hz)✶alpha(8-13Hz) and beta(13-30Hz). The PSD values were then averaged across all epochs for further computations, and topographic power maps for each frequency band were generated.

(2) Resting-State EEG Parameters

☒ Delta/Alpha Power Ratio (DAR)

The DAR represents the ratio between the average delta power and the average alpha power. The DAR for each individual channel c (DAR_c) was calculated first, followed by a whole-brain average, as expressed in Formula (1):

$$DAR_c = \frac{\langle P_c(f) \rangle_{f=1, \dots, 4Hz}}{\langle P_c(f) \rangle_{f=8, \dots, 12Hz}} \quad DAR = \frac{1}{N} \sum_{c=1}^N DAR_c$$

1

Furthermore, the DAR of the affected hemisphere (DAR_{ah}) and the DAR of the unaffected hemisphere (DAR_{uh}) were calculated separately, excluding midline electrodes. The specific electrodes comprising the affected and unaffected hemispheres are illustrated in Fig. 1.

☒ Pairwise-Derived Brain Symmetry Index (pdBSI)

The pdBSI is utilized to quantify the symmetry of electrophysiological activity between homologous brain regions across the left and right hemispheres, with values ranging from 0 (perfect symmetry) to 1 (complete asymmetry). First, the total power within the 1–25 Hz range was calculated for each electrode, excluding midline electrodes. The symmetry index for homologous channel pairs (CP) was computed, followed by a whole-brain average, as delineated in Formula (2):

$$pdBSI_{CP} = \left\langle \left| \frac{P_{C_R}(f) - P_{C_L}(f)}{P_{C_R}(f) + P_{C_L}(f)} \right| \right\rangle_{f=1, \dots, 25Hz} \quad pdBSI = \frac{2}{N} \sum_{CP=1}^{N/2} pdBSI_{CP}$$

2

Additionally, the pdBSI for the four distinct frequency bands across the whole brain, as well as the pdBSI for the alpha band specifically in the parieto-occipital region (parieto-occipital), were calculated. The parieto-occipital region included electrodes P1, P2, P3, P4, P5, P6, P7, P8, PO3, PO4, PO5, PO6, PO7, PO8, O1, and O2, as depicted in Fig. 1.

☒ Weighted Phase Lag Index (wPLI)

The wPLI is an extension of the Phase Lag Index (PLI), weighted by the magnitude of the imaginary component of the cross-spectrum. A Current Source Density (CSD) transformation was applied to the preprocessed EEG data to mitigate volume conduction effects and enhance the spatial resolution of the EEG signals. Subsequently, bandpass filtering was applied, and the Hilbert transform was utilized to extract the analytic signal. Consistent with the methodology of Yordanova et al. [11], eight electrodes within the frontoparietal network were selected (dorsal frontal: F3, F4; ventral frontal: F7, F8; dorsal

parietal: P3, P4; ventral parietal: P7, P8). The wPLI between each electrode pair was computed using the formula provided by Vinck et al. [12]. The wPLI value ranges from 0 to 1; a higher wPLI denotes a stronger degree of phase coupling in neural oscillatory activity, with 1 indicating maximal functional connectivity.

2.4 Event-Related Potential Acquisition and Analysis

(1) ERP Task

The ERP task was programmed using E-Prime 2.0, with stimuli presented on a computer monitor. The stimulus sequence consisted of a background, a cue, and a target stimulus. This task paradigm is identical to the one employed in the study by Ye et al. [13], as depicted in Fig. 2. Participants were seated at a viewing distance of 57 cm from the display screen. The sequence of a single trial proceeded as follows:

- ☒ Fixation period: A central fixation cross "+" ($0.4^{\circ} \times 0.4^{\circ}$) and bilateral rectangular frames ($11.4^{\circ} \times 1.7^{\circ}$) were presented on the screen for 800 – 1000 ms.
- ☒ Cue period: The central fixation cross changed to a yellow arrow cue (" $<$ " or " $>$ "), which was displayed for 1400 – 1800 ms. Participants were explicitly informed that the direction of the cue might or might not predict the location of the subsequent target stimulus.
- ☒ Target period: A target stimulus "*" appeared within either the left or right rectangular frame for 100 ms.
- ☒ Response period: Upon detecting the target stimulus, participants were required to respond as quickly and accurately as possible via a mouse button press (left click for a left-sided target, right click for a right-sided target). The response time window was 1200 ms. The inter-trial interval (ITI) was set to 1000 ms.

The ERP task comprised 16 blocks (referred to as sessions in the original text), with 40 trials per block, yielding a total of 640 trials. The ratio of valid cues (where the cue direction matched the target location) to invalid cues (where the cue direction was opposite to the target location) was 80% to 20%. Accuracy was defined as the percentage of trials with correct mouse responses relative to the total number of trials. Response time (RT) was defined as the temporal interval between target onset and the participant's mouse click. Prior to the task, participants were instructed that both accuracy and speed were equally important. Rest breaks were permitted between blocks.

(2) ERP Data Acquisition and Analysis

During the ERP task, EEG data were recorded synchronously using a 64-channel Neuroscan system (Compumedics USA, Ltd., El Paso, TX, USA). Electrodes were positioned according to the international 10–20 system, and signals were digitized at a sampling rate of 1000 Hz. All signals were amplified utilizing a 0.05 – 100 Hz bandpass filter. The tip of the nose served as the online reference, and the ground electrode was placed between FPz and Fz. Electrode impedances were maintained below 10 k Ω .

Offline EEG preprocessing was conducted using the open-source EEGLAB v13.0 toolbox within the MATLAB 2013b environment (MathWorks, Natick, MA, USA). Initially, a bandpass filter (0.1 – 40 Hz) and a notch filter (49 – 51 Hz) were applied to the continuous EEG data. The data were then segmented into epochs ranging from – 200 ms to 800 ms relative to the target stimulus onset, with the – 200 ms to 0 ms pre-stimulus period utilized for baseline correction. Subsequently, artifact-contaminated channels were interpolated, bad epochs were manually rejected, and the data were re-referenced to the whole-brain average reference. Independent Component Analysis (ICA) was then applied to identify and remove ocular artifacts (e.g., blinks and eye movements). Finally, epochs with voltage amplitudes exceeding $\pm 100\mu\text{V}$ and epochs corresponding to incorrect behavioral responses were discarded; only epochs from correct trials were retained for further analysis.

The EEG waveforms for valid and invalid cue conditions were averaged separately. The latency and amplitude of the P300 component were extracted from electrodes P3 and P4. The P300 component was defined as the prominent positive-going deflection occurring approximately 300 ms post-target onset. The P300 amplitude (μV) was quantified as the maximum peak amplitude within the specified time window, and the P300 latency (ms) was defined as the time interval from target onset to this maximum peak.

2.5 Treatment Protocol

(1) Determination of Resting Motor Threshold (RMT)

A Magstim Rapid2 transcranial magnetic stimulator (Magstim Company, Whitland, Carmarthenshire, UK) equipped with a figure-of-8 coil (outer diameter: 87 mm, peak magnetic field: 2.0 Tesla, pulse duration: 250 μs) was utilized. Single-pulse TMS was applied to the hand motor cortex representation of the unaffected hemisphere. While the target muscle remained completely relaxed, motor evoked potentials (MEPs) were recorded using a Nicolet VikingQuest electromyography (EMG) system. Surface electrodes were placed over the muscle belly of the contralateral abductor pollicis brevis (APB). The coil position was systematically fine-tuned to identify the "hotspot," defined as the stimulation site that elicited MEPs with the maximum peak-to-peak amplitude and the shortest latency. Subsequently, the stimulator output intensity was gradually decreased to determine the minimum intensity required to evoke an MEP of at least 50 μV in ≥ 5 out of 10 consecutive trials. This intensity was defined as the RMT.

(2) iTBS Treatment Protocol

iTBS Group: An intermittent theta burst stimulation (iTBS) paradigm was administered. The protocol consisted of 2-second trains of stimulation followed by an 8-second inter-train interval, repeated for 20 cycles per session. Each train comprised bursts of 3 pulses delivered at 30 Hz, with the bursts repeated at an inter-burst interval of 200 ms (i.e., a 5 Hz theta rhythm). Each session delivered a total of 600 pulses over a duration of 190 seconds, as illustrated in Fig. 3. Patients received 2 sessions per day, 5 days per week, for a total of 20 sessions.

Stimulation intensity: 80% of the RMT.

Stimulation site: Electrode position F5 over the unaffected hemisphere, corresponding to the surface projection of the dorsolateral prefrontal cortex (DLPFC) in the intact hemisphere. The coil was held tangentially to the scalp at the stimulation site, with the handle pointing directly backward.

Sham Stimulation Group: For sham stimulation, the coil was tilted at a 90° angle relative to the scalp, resting on its edge, and the stimulation intensity was reduced to 40% of the RMT. The frequency of sessions was identical to the iTBS group (2 sessions/day, 5 days/week, 20 sessions in total).

(3) Conventional Rehabilitation Therapy

All patients received conventional rehabilitation therapy administered by certified rehabilitation therapists. This primarily included one-on-one manual motor function training, occupational therapy, and visual scanning training. Each specific training modality lasted for 30 minutes, administered twice daily, 5 days per week.

(4) Adverse events

Throughout the treatment period, patients were instructed to report any adverse events occurring during or immediately after the stimulation, including drowsiness, headache, seizures, facial discomfort, syncope, and phosphenes. All reported events were systematically documented. In the event of pain, pain intensity was assessed using the Visual Analogue Scale (VAS).

2.6 Statistical Analysis

Data analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Categorical data were analyzed using the Chi-square (χ^2) test. Continuous data are expressed as the mean $\pm$ standard deviation ($\bar{x} \pm s$). Within-group comparisons (pre- versus post-treatment) were evaluated using paired-sample t-tests, whereas between-group comparisons were analyzed utilizing independent-sample t-tests. The threshold for statistical significance was set at $P < 0.05$.

3. Results

3.1 Baseline Characteristics

A total of 39 patients with visuospatial neglect (VSN) were enrolled in this study, comprising 20 patients in the iTBS group and 19 in the sham stimulation group. Table 1 presents the demographic and clinical characteristics of the two groups. Statistical analysis revealed no significant differences between the groups regarding baseline variables, including age, sex, stroke type, time since stroke onset, BI score, FMA score, BBS score, and baseline Line Bisection Test score (all $P > 0.05$).

Throughout the experiment, TMS was well-tolerated by patients in both groups. No transient or long-term adverse events, including dizziness or mild headaches, were reported.

Table 1
Patients' demographic and clinical characteristics

Gender (female:male)	iTBS group(n = 20)	Sham-stimulation group(n = 19)	t/ χ^2	P
	15:5	15:4	0.086	0.770
– Age(years, $\chi \pm s$)	55.60 $\pm$ 10.76	55.63 $\pm$ 9.57	-0.01	0.992
– Poststroke time (day, $\chi \pm s$)	27.60 $\pm$ 9.21	24.89 $\pm$ 17.33	0.613	0.544
Type of stroke (Ischemic: Hemorrhagic)	19:1	16:3	0.339	0.560
Lesion location (Cortical: Cortico-subcortical: Subcortical)	1:15:4	1:13:5	0.228	0.892
– BI($\chi \pm s$)	34.00 $\pm$ 12.73	33.68 $\pm$ 11.41	0.081	0.936
– FMA($\chi \pm s$)	29.65 $\pm$ 13.13	30.05 $\pm$ 17.14	-0.083	0.935
– BBS($\chi \pm s$)	8.50 $\pm$ 8.79	6.89 $\pm$ 8.38	0.583	0.563
– LBE(%, $\chi \pm s$)	35.36 $\pm$ 20.80	41.47 $\pm$ 18.00	-0.979	0.334
– ORL(%, $\chi \pm s$)	39.17 $\pm$ 24.82	40.53 $\pm$ 24.15	-0.173	0.334
– ORS(%, $\chi \pm s$)	42.49 $\pm$ 17.91	45.39 $\pm$ 24.41	-0.426	0.673

3.2 Behavioral Pen-and-Paper Assessments

As detailed in Tables 2 to 4, within-group comparisons revealed significant post-treatment reductions in scores for the Line Bisection Test (LBT), Line Cancellation Test (LCT), and Star Cancellation Test (SCT) in

both groups compared to baseline (all $P < 0.05$), indicating an improvement in VSN symptoms.

At baseline, there were no significant between-group differences in the LBT, LCT, or SCT scores (all $P > 0.05$). Following treatment, however, the absolute post-treatment scores, as well as the pre- to post-treatment change scores (Δ) for all three behavioral assessments, differed significantly between the iTBS and sham groups (all $P < 0.05$).

Table 2

Comparison of LBT scores between the two groups ($\%$, $\chi \pm s$)

iTBS group	n	Pre-treatment	Post-treatment	Change score(Δ)	t	P
	20	35.36 $\pm$ 20.80	14.12 $\pm$ 16.61***	21.24 $\pm$ 7.33	12.955	< 0.001
Sham-stimulation group	19	41.47 $\pm$ 18.00	35.89 $\pm$ 16.93***	5.58 $\pm$ 4.61***	5.272	< 0.001
t		-0.979	-4.054	7.938		
P		0.334	< 0.001	< 0.001		
⊠: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$						

Table 3

Comparison of LCT scores between the two groups ($\%$, $\chi \pm s$)

iTBS group	n	Pre-treatment	Post-treatment	Change score(Δ)	t	P
	20	39.17 $\pm$ 24.82	17.67 $\pm$ 19.68	21.50 $\pm$ 7.53	12.768	< 0.001
Sham-stimulation group	19	40.53 $\pm$ 24.15	31.40 $\pm$ 21.64	9.12 $\pm$ 6.65	5.977	< 0.001
t		-0.173	-2.076	5.428		
P		0.863	0.45	< 0.001		
⊠: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$						

Table 3

Comparison of SCT scores between the two groups (% $\chi \pm s$)

iTBS group	n	Pre-treatment	Post-treatment	Change score(Δ)	t	P
	20	42.49 $\pm$ 17.91	21.25 $\pm$ 15.04	21.24 $\pm$ 5.45	17.430	< 0.001
Sham-stimulation group	19	45.39 $\pm$ 24.41	36.28 $\pm$ 24.85	9.12 $\pm$ 5.58	7.122	< 0.001
t		-0.426	-2.299	6.864		
P		0.673	0.27	< 0.001		
⊠: *P < 0.05; **P < 0.01; ***P < 0.001						

3.3 Resting-State EEG Parameters

(1) DAR

As illustrated in Fig. 4, within-group comparisons for the iTBS group showed significant decreases in the global DAR, affected hemisphere DAR (DARah), and unaffected hemisphere DAR (DARuh) post-treatment compared to baseline (all $P < 0.001$). Conversely, as shown in Fig. 4B, the sham stimulation group exhibited significant post-treatment decreases only in the global DAR and DARah (all $P < 0.001$), with no significant change observed in the DARuh ($P > 0.05$).

At baseline, no significant differences were found between the two groups in the global DAR, DARah, or DARuh (all $P > 0.05$). Post-treatment, between-group comparisons revealed statistically significant differences across all three DAR metrics (all $P < 0.05$).

(2) pdBSI

As shown in Fig. 5 within-group comparisons revealed no significant changes in pdBSI values from baseline to post-treatment in either group (all $P > 0.05$). Furthermore, between-group comparisons indicated no significant differences in pdBSI values either before or after treatment (all $P > 0.05$).

(3) Topographic Maps

Figure 6 illustrates the topographic distribution of alpha-band spectral power before and after treatment for both groups. Compared to baseline, the iTBS group exhibited a pronounced increase in alpha-band power within the right parieto-occipital region post-treatment. In contrast, the sham stimulation group showed only a slight, non-significant elevation in alpha power in the corresponding region.

(4) wPLI

Figure 7 presents the alpha-band wPLI results for both groups. Compared to baseline, the iTBS group demonstrated a significant post-treatment increase in alpha-band wPLI (functional connectivity) between electrode pairs F3-P4 and P3-P4 (all $P < 0.05$). In the sham stimulation group, a significant post-treatment increase in alpha-band wPLI was observed exclusively between the P3-P4 electrode pair (all $P < 0.05$).

3.4 Behavioral and ERP Results During the Attention Task

(1) Accuracy and Response Time

A total of 17 patients in the iTBS group and 16 patients in the sham stimulation group successfully completed the ERP task. Figure 8 illustrates the comparisons of task accuracy and response time (RT) before and after treatment for both groups.

As depicted in Figs. 8A and 8B, within-group comparisons revealed that post-treatment accuracy was significantly improved in both groups for overall trials, as well as for left valid, left invalid, and right invalid cues compared to baseline (all $P < 0.05$). However, accuracy for right valid cues showed no significant change from pre- to post-treatment ($P > 0.05$).

As shown in Figs. 8C and 8D, post-treatment RTs in both groups were significantly reduced across all conditions—including overall RT, and RTs for left valid, right valid, left invalid, and right invalid cues—compared to baseline (all $P < 0.05$).

At baseline, between-group comparisons revealed no significant differences in either accuracy or RT across any condition (all $P > 0.05$). Following treatment, however, significant between-group differences were observed in overall accuracy, overall RT, left valid cue accuracy, left valid cue RT, left invalid cue accuracy, and left invalid cue RT (all $P < 0.05$).

(2) P300 Component

Figure 9 presents the grand-averaged P300 waveforms elicited under the left valid cue condition before and after treatment for both groups. Under this condition, within-group comparisons indicated that the P300 amplitude at electrode P3 increased significantly post-treatment compared to baseline in both groups, whereas the P300 latency remained unchanged. At electrode P4, neither the P300 amplitude nor latency exhibited significant changes pre- to post-treatment ($P > 0.05$).

4. Discussion

In this study, we evaluated patients with post-stroke visuospatial neglect (VSN) using resting-state EEG and task-related ERPs before and after iTBS treatment to investigate the modulatory effects of iTBS on cortical electrical activity. Our findings demonstrate that excitatory iTBS applied to the dorsolateral prefrontal cortex (DLPFC) of the unaffected hemisphere significantly increases alpha-band spectral power in the right parieto-occipital region, enhances interhemispheric functional connectivity within the

parietal alpha band, and amplifies the P300 amplitude in the unaffected hemisphere. These neurophysiological changes were accompanied by a significant amelioration of neglect symptoms in patients during the subacute phase of right-hemispheric stroke. Crucially, these results provide compelling evidence that the unaffected hemisphere plays an active, compensatory role in the recovery of VSN. Furthermore, our findings underscore the utility of combining resting-state EEG and task-related ERPs as robust, multidimensional biomarkers for evaluating the neuromodulatory efficacy of non-invasive brain stimulation.

Currently, there is an ongoing debate regarding the optimal TMS treatment protocols for VSN and their underlying mechanisms of recovery. The traditional "interhemispheric competition model" posits that the overactive unaffected hemisphere must be inhibited to restore interhemispheric balance. However, a growing body of recent neuroimaging and animal studies has challenged this dogma, revealing that post-stroke attention networks undergo large-scale reorganization not only in the lesioned hemisphere but also in the intact hemisphere, which plays a pivotal compensatory role in functional recovery[14–16]. When the capacity for neuronal reorganization in the affected hemisphere is severely compromised, the unaffected hemisphere may take the dominant role in compensating for attentional deficits[17]. In the present study, applying excitatory iTBS to the unaffected DLPFC successfully alleviated VSN symptoms. This aligns with the findings of Ye et al. [143] and Cao et al.[18] providing direct clinical evidence supporting the "unaffected hemisphere compensation hypothesis" and demonstrating that exciting the intact hemisphere is a viable and effective intervention strategy for VSN.

Our EEG analysis revealed that both the global DAR and the DAR of the affected hemisphere significantly decreased post-treatment in both groups. Notably, the DAR of the unaffected hemisphere significantly decreased only following iTBS, with no significant change observed in the sham group. This confirms that TMS effectively modulates the spectral power of resting-state neural oscillations. Rhythmic TMS can interact dynamically with the brain's endogenous oscillatory activity [19]. Initially, neuronal populations may exhibit asynchronous firing patterns. Exogenous rhythmic TMS can drive these neuronal populations to synchronize their firing frequencies with the external stimulus, a phenomenon known as neural entrainment [20]. For instance, Wozniak et al. [21] applied iTBS to the left DLPFC in healthy individuals and observed significant decreases in delta and theta power over left prefrontal electrodes, though alpha power remained unchanged. Conversely, Grossheinrich et al. [22] reported increased alpha power in the left inferior and medial frontal gyri following iTBS to the left DLPFC. Therefore, it is plausible that iTBS reduces the DAR in VSN patients by attenuating delta power, amplifying alpha power, or a combination of both.

Admittedly, some studies have reported null findings regarding TMS-induced changes in resting-state EEG power. Graf et al. [23] observed only marginal changes in delta and theta power following rTMS to the left DLPFC, which likely represented a statistical artifact due to repeated measures. Such discrepancies across studies are likely attributable to heterogeneous TMS protocols. Furthermore, the modulatory effects of TMS on neural oscillations are highly dependent on the stimulation site and intensity. For example, cerebellar TBS modulates alpha and beta power [24] whereas motor cortex cTBS

alters theta, alpha, and beta oscillations [25]. Prefrontal stimulation has also been shown to induce changes in theta power [26], suggesting that TMS effects may be tuned to the intrinsic resonant frequencies of the targeted cortical regions. Additionally, Chung et al. [27] demonstrated an inverted-U relationship between iTBS intensity and cortical reactivity, finding that an intensity of 75% RMT produced optimal electrophysiological changes. Research has also established that rTMS tuned to entrain alpha oscillations can modulate cognitive processes such as working memory and depression [28, 29]. Sauseng et al. [29] found that alpha-rTMS applied to the right parietal lobe significantly enhanced working memory capacity. While some studies suggest that individualized alpha-band TMS yields superior therapeutic outcomes, it remains to be determined whether individualizing TMS frequencies can further optimize treatment parameters and enhance clinical efficacy for VSN patients.

Topographic analysis in the current study revealed a significant post-iTBS increase in alpha-band power over the right parieto-occipital region. TMS not only alters local cortical excitability during the neuronal refractory period but also propagates to remote, functionally interconnected regions within the attention network. This broad activation facilitates neuronal reorganization and compensation by inducing long-term potentiation (LTP) or long-term depression (LTD) of synaptic efficacy. Interhemispheric functional connectivity is integral to VSN recovery; the severity of neglect correlates inversely with connectivity, and clinical recovery is typically accompanied by the restoration of interhemispheric networks [30]. This restoration is evident in patients with favorable VSN outcomes but absent in those with poor recovery, highlighting interhemispheric connectivity as a critical prognostic biomarker. In our study, exciting the unaffected hemisphere with iTBS strengthened the functional connectivity (wPLI) between the right parietal lobe and the left frontal/parietal regions. The bilateral frontoparietal networks are densely interconnected via transcallosal pathways. Thus, iTBS to the unaffected DLPFC likely induces widespread network activation mediated by the corpus callosum. While the sham group exhibited a slight, non-significant increase in frontoparietal alpha connectivity, the iTBS effect was robust. Similarly, Ding et al. [10] reported an immediate increase in resting-state interhemispheric connectivity following iTBS to the affected M1 in stroke patients. This network reorganization, driven by the intact DLPFC, effectively breaks the functional isolation of peri-lesional networks and enhances the synergistic processing of spatial attention across both hemispheres.

During the task-state ERP assessment, we found that iTBS significantly increased the P300 amplitude in the unaffected hemisphere, corroborating previous literature. For example, Price et al. [31] observed a significant elevation in P300 amplitude following single-pulse TMS to the left prefrontal cortex in healthy subjects. Mechanistically, this amplitude enhancement may be driven by TMS-induced modulation of neurotransmitter systems. Neurotransmitters elicit excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs), which form the neurophysiological basis of ERPs. Transcranial magnetic stimulation, particularly over the prefrontal cortex, is known to modulate dopaminergic and glutamatergic transmission—both of which are critical for P300 generation. Excitatory TMS has been shown to elevate glutamate levels in anterior brain regions and stimulate high-frequency dopamine release in the left prefrontal cortex. Dopaminergic function directly influences the allocation of neural resources and the speed of cognitive processing during specific tasks, thereby modulating ERP latency and amplitude.

Consequently, the TMS-induced enhancement of dopaminergic and glutamatergic activity likely underpins the increased P300 amplitude observed in our cohort. It should be noted that some divergent findings exist; Pinto et al. [32] reported shortened P300 latencies but unchanged amplitudes following iTBS to the left DLPFC. This discrepancy is likely due to methodological differences, as Pinto et al. utilized an auditory paradigm in healthy volunteers, whereas our study employed a visual spatial attention paradigm specifically designed for stroke patients with VSN.

Several limitations of this study must be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of the findings. Second, the study lacked a longitudinal follow-up. TMS-induced neuroplastic changes—potentially mediated by enhanced NMDA receptor activation [33] and increased neuronal survival in peri-infarct regions [34]—can persist for up to three months [35]; future studies should evaluate the long-term durability of these effects. Third, we did not control for or analyze variations in lesion volume, which could independently influence EEG topography and connectivity metrics. Finally, a detailed, quantitative assessment of baseline cognitive function was not performed. A patient's cognitive reserve may significantly dictate their trajectory of cognitive recovery and their neurophysiological responsiveness to TMS interventions. Future large-scale, longitudinal trials incorporating comprehensive neuroimaging and cognitive profiling are warranted to address these limitations.

Conclusion

This study demonstrates that excitatory intermittent theta burst stimulation (iTBS) applied to the unaffected DLPFC significantly ameliorates clinical symptoms in patients with subacute post-stroke visuospatial neglect. The underlying neurophysiological mechanisms involve not only a reduction in the resting-state DAR and an increase in alpha-band oscillatory power in the right parieto-occipital region, but also a significant enhancement in interhemispheric functional connectivity within the frontoparietal network. Furthermore, task-related ERPs revealed an increased P300 amplitude in the unaffected hemisphere, reflecting the effective reallocation of cognitive and attentional resources. These findings provide direct electrophysiological evidence supporting the "unaffected hemisphere compensation hypothesis," highlighting the active and pivotal role of the intact hemisphere in post-stroke network reorganization. Additionally, this study establishes that the integration of resting-state EEG and task-related ERPs serves as a robust and reliable biomarker for evaluating the neuromodulatory efficacy of non-invasive brain stimulation. Future research should build upon these findings to explore precise, individualized neuromodulation strategies based on patient-specific EEG characteristics.

Declarations

Ethics declarations

Ethics approval and consent to participate

Ethics approval for the collection of demographics, and clinical and treatment data of all participants was obtained from the Institutional Review Board of Xuanwu Hospital, Capital Medical University (ID: [2023]052). Written informed consent was obtained from all participants prior to enrollment. This study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry under the code ChiCTR2500100355: <https://www.chictr.org.cn/index.html>. Registered on April 8, 2025.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Number 82272593). The funding sources had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit this article for publication.

Author Contribution

Conception and design: YC.Z, LL.Y. Acquisition of data: YC.Z, WY.Z. Statistical analysis: YX.X. Drafting the article: YC.Z. Critically revising the article: WQ.S, L.C, LL.Y. Study supervision: L.C, LL.Y.

Acknowledgement

We would like to thank all our participants for their interest and time investment.

Data Availability

The raw de-identified data supporting the findings of this study are available from the corresponding author(s) upon reasonable request.

References

1. Hammerbeck, U., et al., *Spatial Neglect in Stroke: Identification, Disease Process and Association with Outcome During Inpatient Rehabilitation*. Brain Sci, 2019. 9(12).

2. Linden, T., et al., *Visual neglect and cognitive impairment in elderly patients late after stroke*. Acta Neurol Scand, 2005. 111(3): p. 163–8.
3. Nijboer, T.C., B.J. Kollen, and G. Kwakkel, *Time course of visuospatial neglect early after stroke: a longitudinal cohort study*. Cortex, 2013. 49(8): p. 2021–7.
4. Zhao, R., et al., *Effect of noninvasive brain stimulation for unilateral spatial neglect after stroke: a systematic review and meta-analysis*. J Neurol, 2026. 273(4).
5. Yang, W., et al., *Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients*. J Neurol Sci, 2015. 359(1–2): p. 219–25.
6. Mak, J., et al., *A scalable EEG-based spatial neglect detection system in augmented reality for stroke patients*. J Neurosci Methods, 2026. 432: p. 110756.
7. Fu, W., et al., *Continuous theta-burst stimulation may improve visuospatial neglect via modulating the attention network: a randomized controlled study*. Top Stroke Rehabil, 2017. 24(4): p. 236–241.
8. Haddadshargh, G., et al., *Brain Network Connectivity During Resting-State and a Visuospatial Task as a Biomarker for Spatial Neglect in Stroke Patients*. Neurorehabil Neural Repair, 2026: p. 15459683261419423.
9. Mariner, J., T. Loetscher, and B. Hordacre, *Parietal Cortex Connectivity as a Marker of Shift in Spatial Attention Following Continuous Theta Burst Stimulation*. Front Hum Neurosci, 2021. 15: p. 718662.
10. Ding, Q., et al., *The Effects of Intermittent Theta Burst Stimulation on Functional Brain Network Following Stroke: An Electroencephalography Study*. Front Neurosci, 2021. 15: p. 755709.
11. Yordanova, J., et al., *Synchronization of fronto-parietal beta and theta networks as a signature of visual awareness in neglect*. Neuroimage, 2017. 146: p. 341–354.
12. Vinck, M., et al., *An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias*. Neuroimage, 2011. 55(4): p. 1548–65.
13. Ye, L., et al., *Visual processing features in patients with visual spatial neglect recovering from right-hemispheric stroke*. Neurosci Lett, 2020. 714: p. 134528.
14. Nyffeler, T., et al., *Theta burst stimulation in neglect after stroke: functional outcome and response variability origins*. Brain, 2019. 142(4): p. 992–1008.
15. Ramsey, L.E., et al., *Behavioural clusters and predictors of performance during recovery from stroke*. Nat Hum Behav, 2017. 1.
16. Winters, C., et al., *Generalizability of the Maximum Proportional Recovery Rule to Visuospatial Neglect Early Poststroke*. Neurorehabil Neural Repair, 2017. 31(4): p. 334–342.
17. Hansenne, M., et al., *Impact of low frequency transcranial magnetic stimulation on event-related brain potentials*. Biol Psychol, 2004. 67(3): p. 331–41.
18. Cao, L., et al., *Intermittent theta burst stimulation modulates resting-state functional connectivity in the attention network and promotes behavioral recovery in patients with visual spatial neglect*. Neuroreport, 2016. 27(17): p. 1261–1265.

19. Thut, G., et al., *Rhythmic TMS causes local entrainment of natural oscillatory signatures*. Curr Biol, 2011. 21(14): p. 1176–85.
20. Hanslmayr, S., N. Axmacher, and C.S. Inman, *Modulating Human Memory via Entrainment of Brain Oscillations*. Trends Neurosci, 2019. 42(7): p. 485–499.
21. Wozniak-Kwasniewska, A., et al., *Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects*. Neuroimage, 2014. 88: p. 91–9.
22. Grossheinrich, N., et al., *Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram*. Biol Psychiatry, 2009. 65(9): p. 778–84.
23. Graf, T., et al., *High frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral cortex: EEG topography during waking and subsequent sleep*. Psychiatry Res, 2001. 107(1): p. 1–9.
24. Casula, E.P., et al., *Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas*. Sci Rep, 2016. 6: p. 36191.
25. Vernet, M., et al., *Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG*. Eur J Neurosci, 2013. 37(4): p. 598–606.
26. Chung, S.W., et al., *Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study*. Clin Neurophysiol, 2017. 128(7): p. 1117–1126.
27. Chung, S.W., et al., *Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance*. Hum Brain Mapp, 2018. 39(2): p. 783–802.
28. Zrenner, B., et al., *Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS*. Brain Stimul, 2020. 13(1): p. 197–205.
29. Sauseng, P., et al., *Brain oscillatory substrates of visual short-term memory capacity*. Curr Biol, 2009. 19(21): p. 1846–52.
30. Ye, L., et al., *Analysis of recovery-related white matter microstructures in visual spatial neglect based on diffusion tensor imaging*. Brain Imaging Behav, 2026. 20(1): p. 17.
31. Price, G.W., *EEG-dependent ERP recording: using TMS to increase the incidence of a selected pre-stimulus pattern*. Brain Res Brain Res Protoc, 2004. 12(3): p. 144–51.
32. Pinto, N., et al., *Bilateral theta-burst magnetic stimulation influence on event-related brain potentials*. PLoS One, 2018. 13(1): p. e0190693.
33. Wang, H.Y., et al., *Repetitive transcranial magnetic stimulation enhances BDNF-TrkB signaling in both brain and lymphocyte*. J Neurosci, 2011. 31(30): p. 11044–54.
34. Lefaucheur, J.P., *Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS)*. Neurophysiol Clin, 2006. 36(3): p. 105–15.
35. Du, J., et al., *Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial*. Clin Neurophysiol, 2016. 127(3): p. 1907–13.

Figures

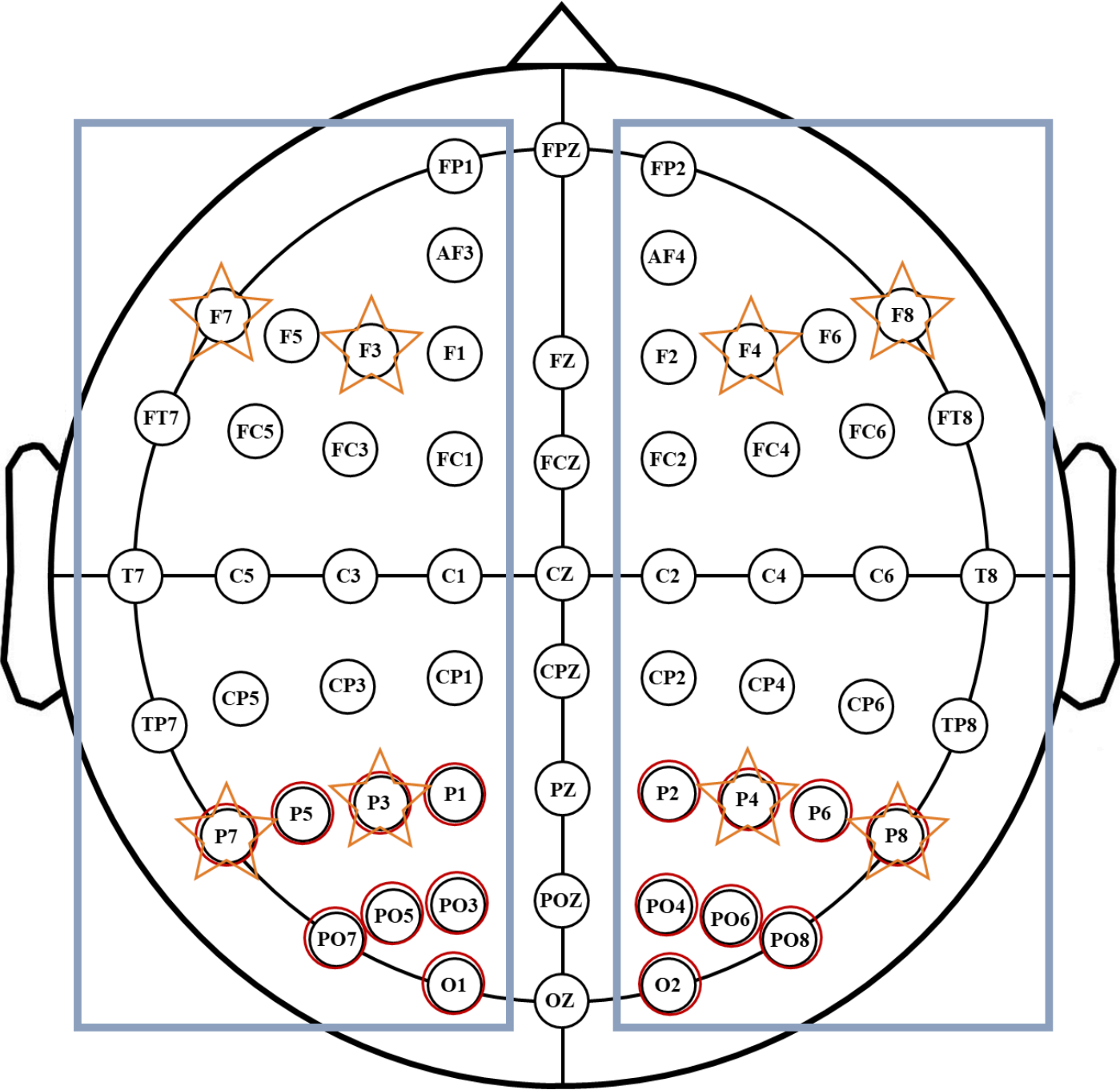


Figure 1

Whole-brain 10-20 EEG topographic map. Blue rectangles indicate the electrodes included for calculating the DAR of the unaffected and affected hemispheres; red circles indicate the electrodes comprising the parieto-occipital region; yellow stars indicate the eight selected electrodes within the frontoparietal network.

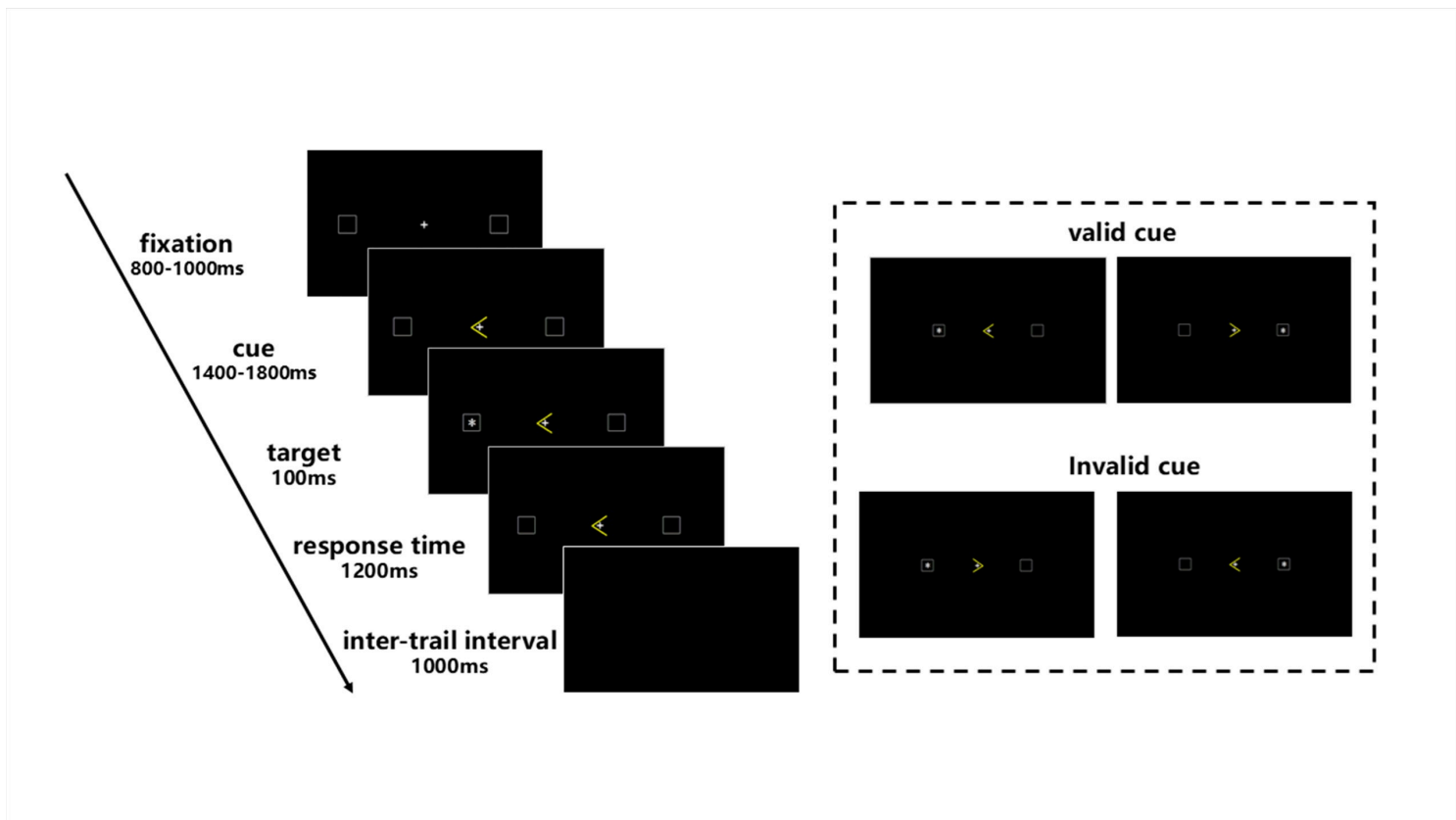


Figure 2

ERP Task Paradigm

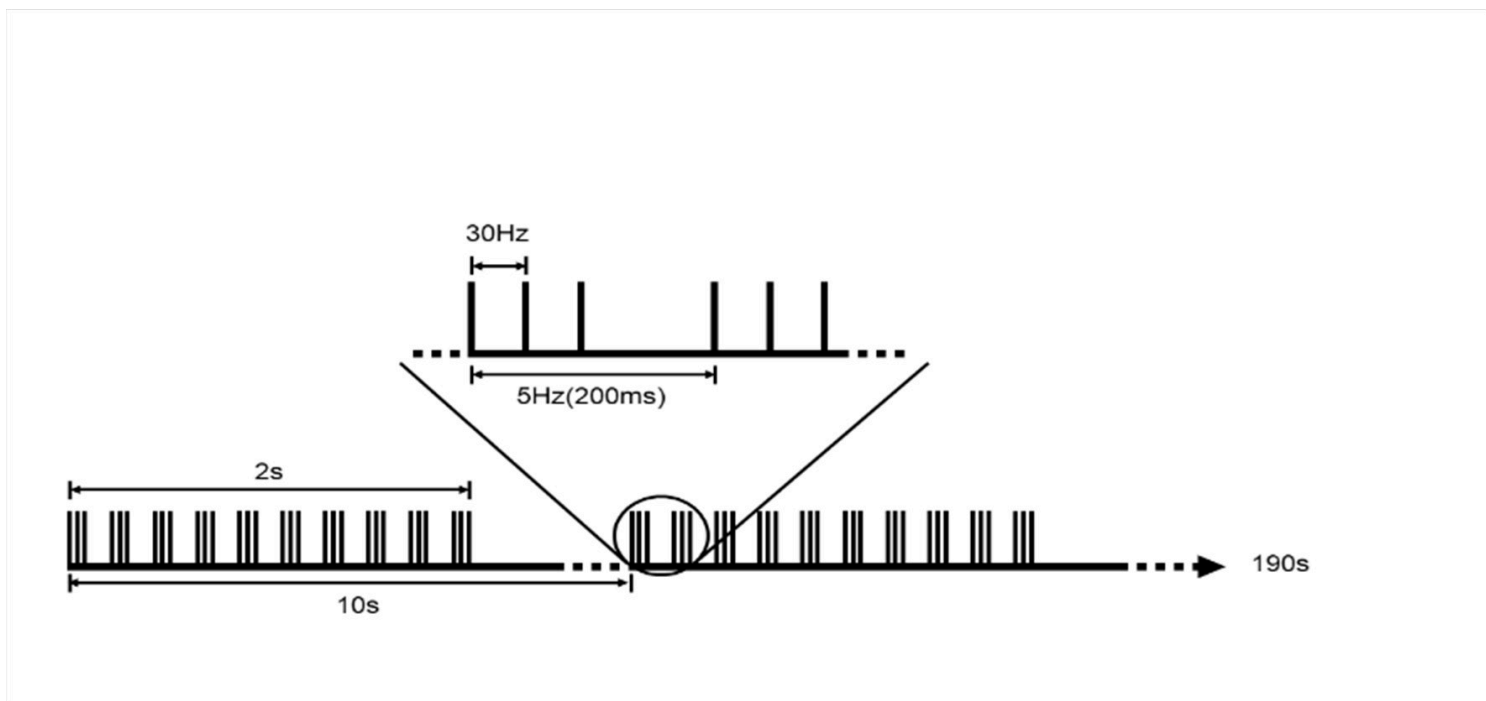


Figure 3

Schematic diagram of the stimulation protocol for the iTBS group.

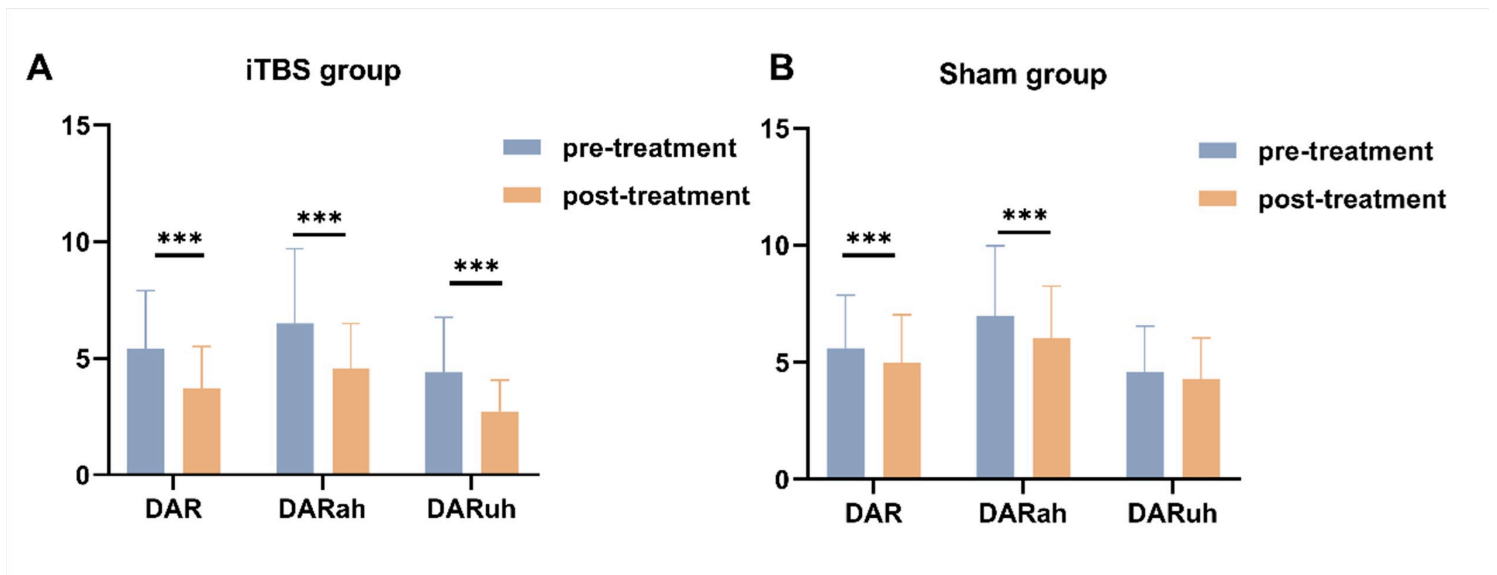


Figure 4

Pre- and post-treatment comparisons of DAR, DARah, and DARuh between the two groups. *** $P < 0.001$.

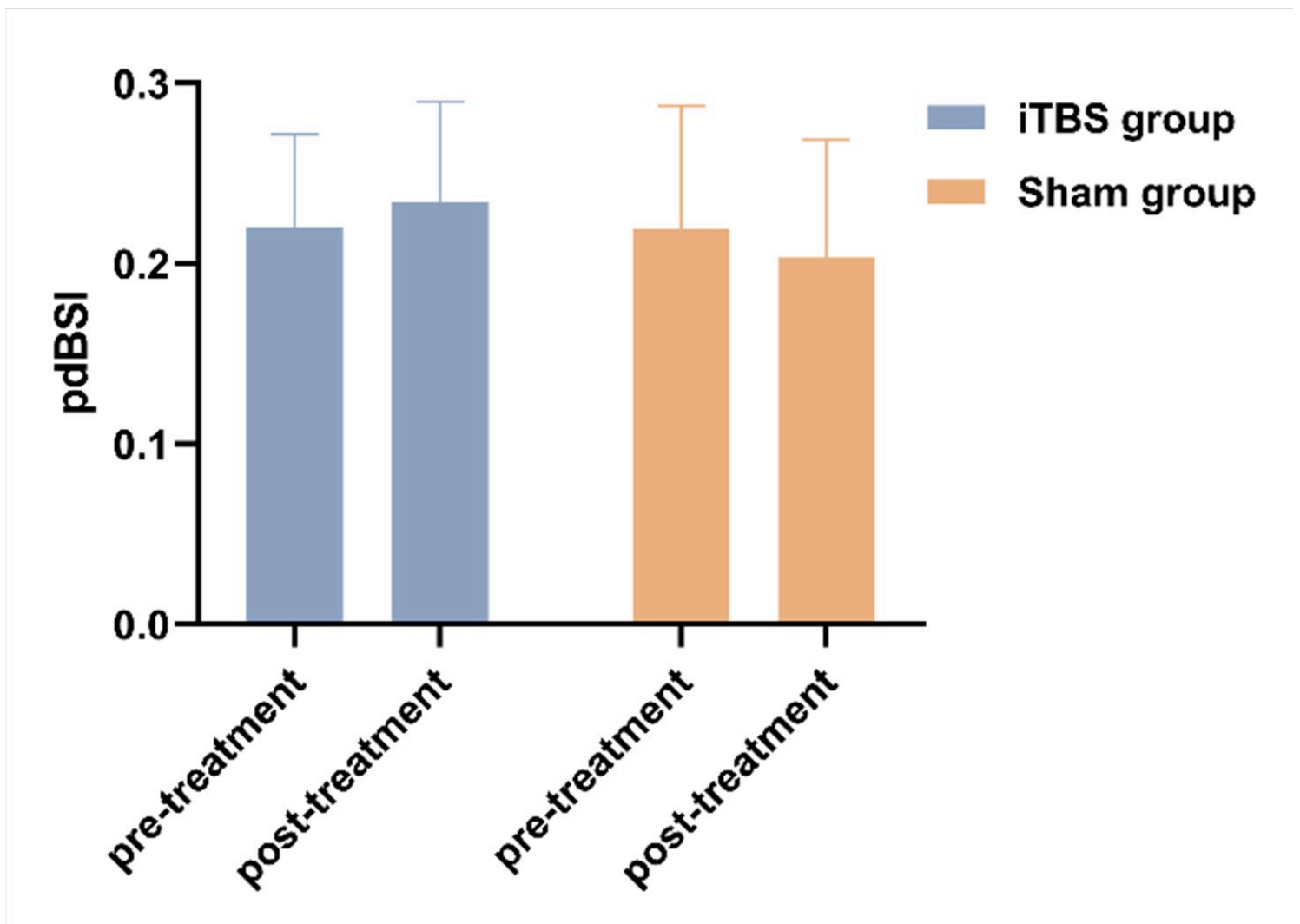


Figure 5

Pre- and post-treatment comparison of pdBSI values in the two groups.

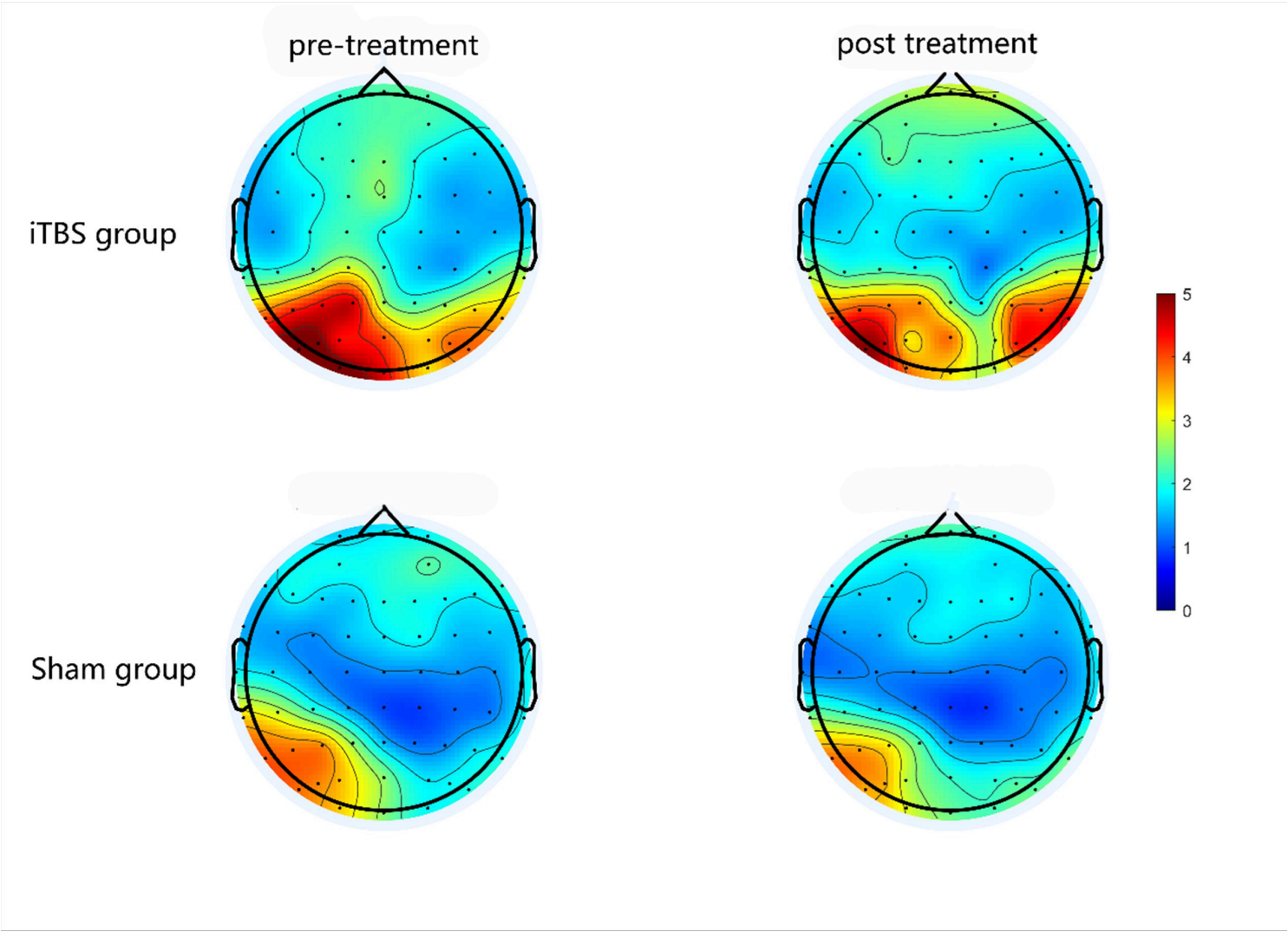


Figure 6

Topographic distribution of alpha-band power before and after treatment in the two groups.

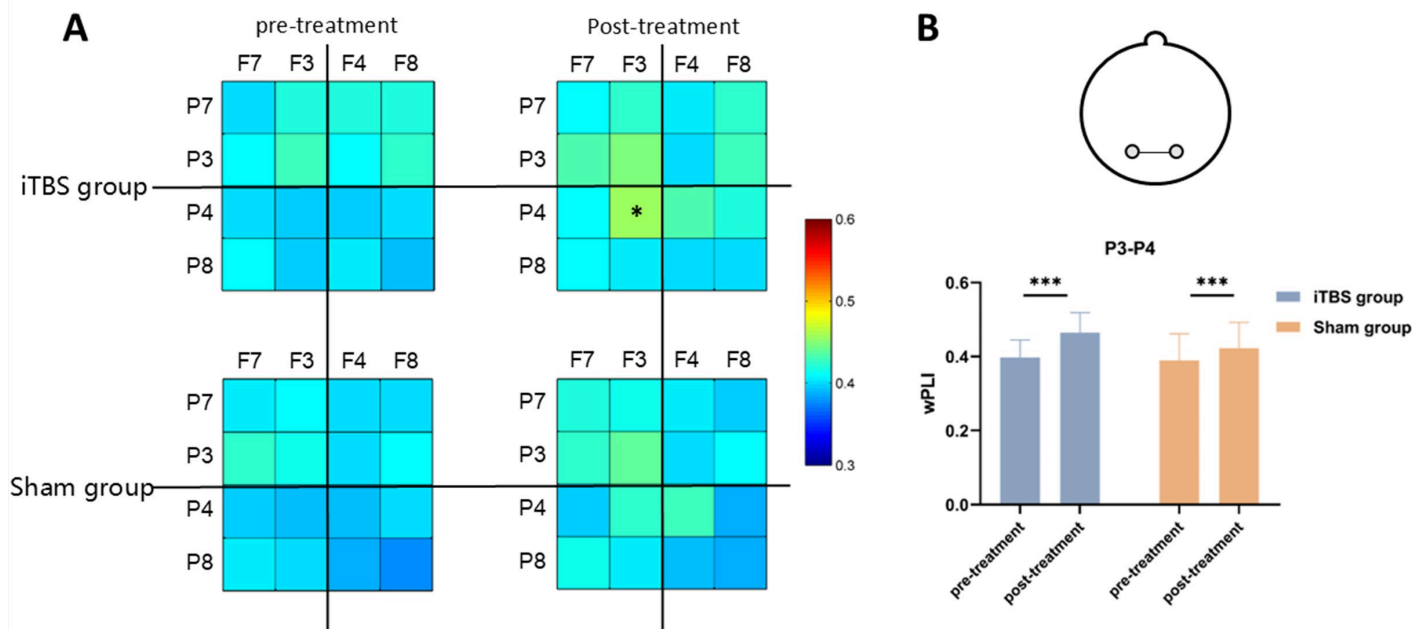


Figure 7

Alpha-band wPLI results of both groups. (A) Mean wPLI comparisons between frontal (x-axis) and parietal (y-axis) electrodes in bilateral hemispheres before and after treatment for the iTBS and sham groups. Significant pre- to post-treatment differences are marked with *. (B) Comparison of the interhemispheric parietal electrode pair P3-P4 before and after treatment in both groups. *** $P < 0.001$.

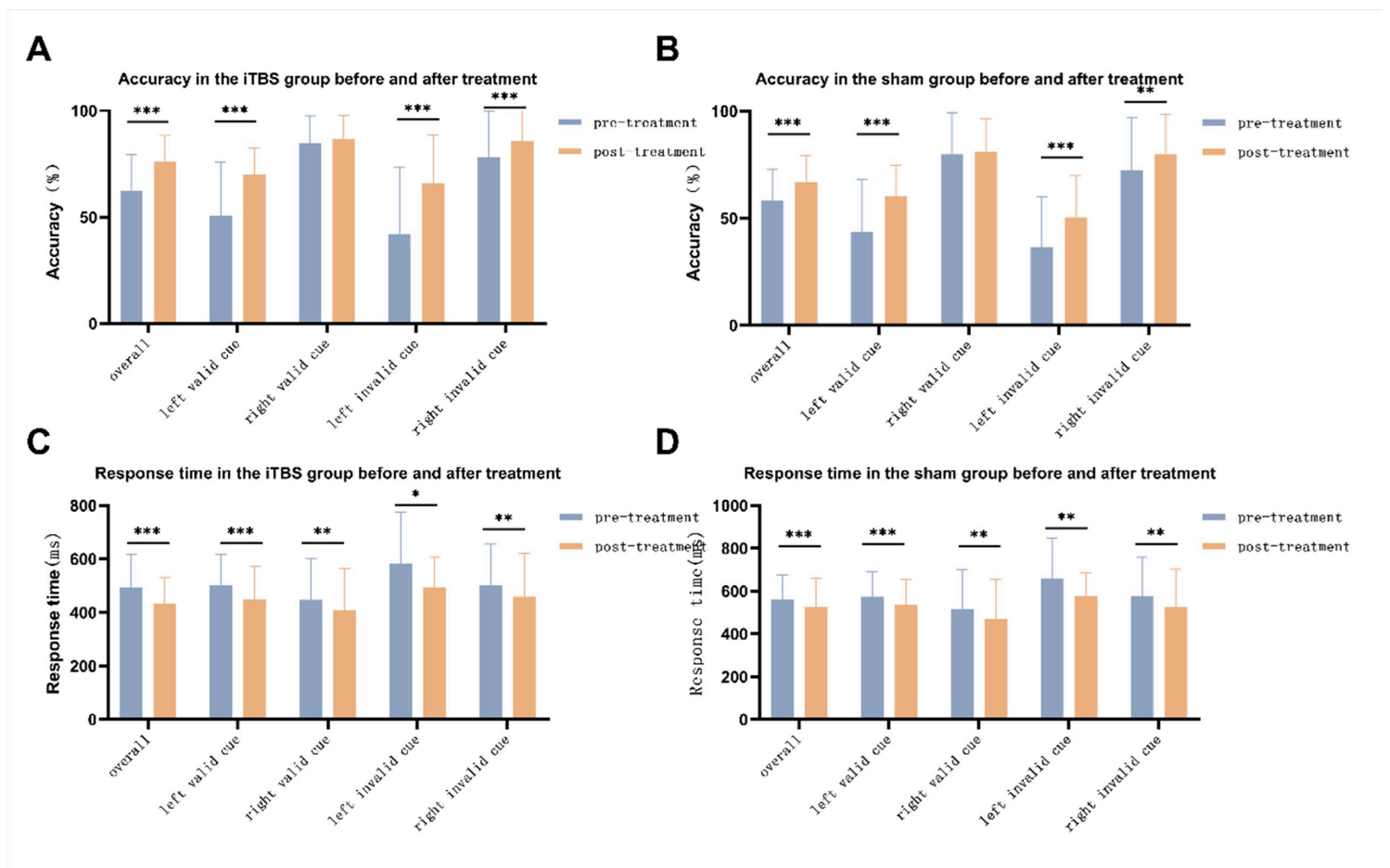


Figure 8

Pre- and post-treatment comparison of ERP task accuracy and response time in both groups. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

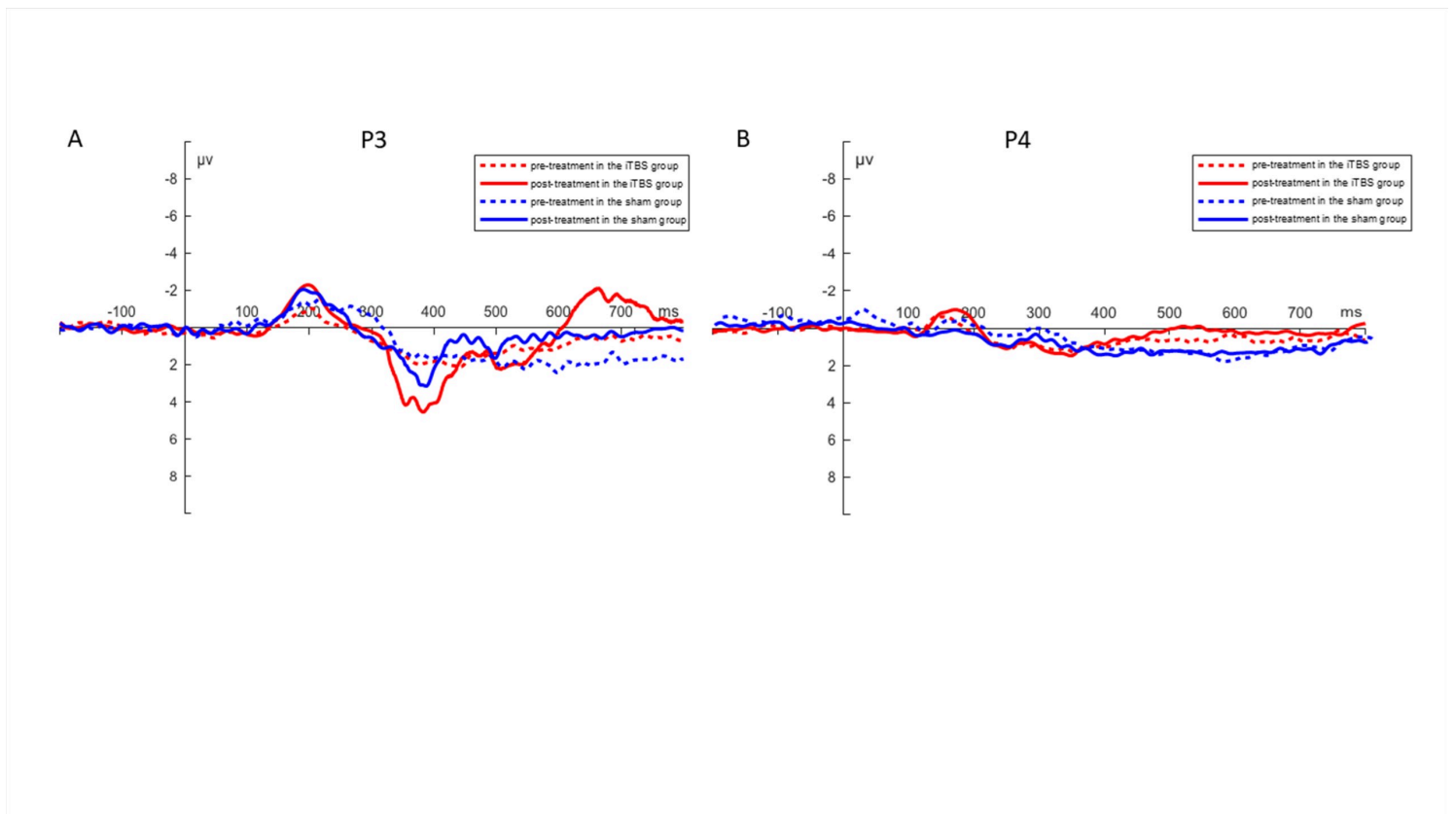


Figure 9

Comparison of grand-averaged P300 waveforms elicited by left valid cues before and after treatment in both groups.

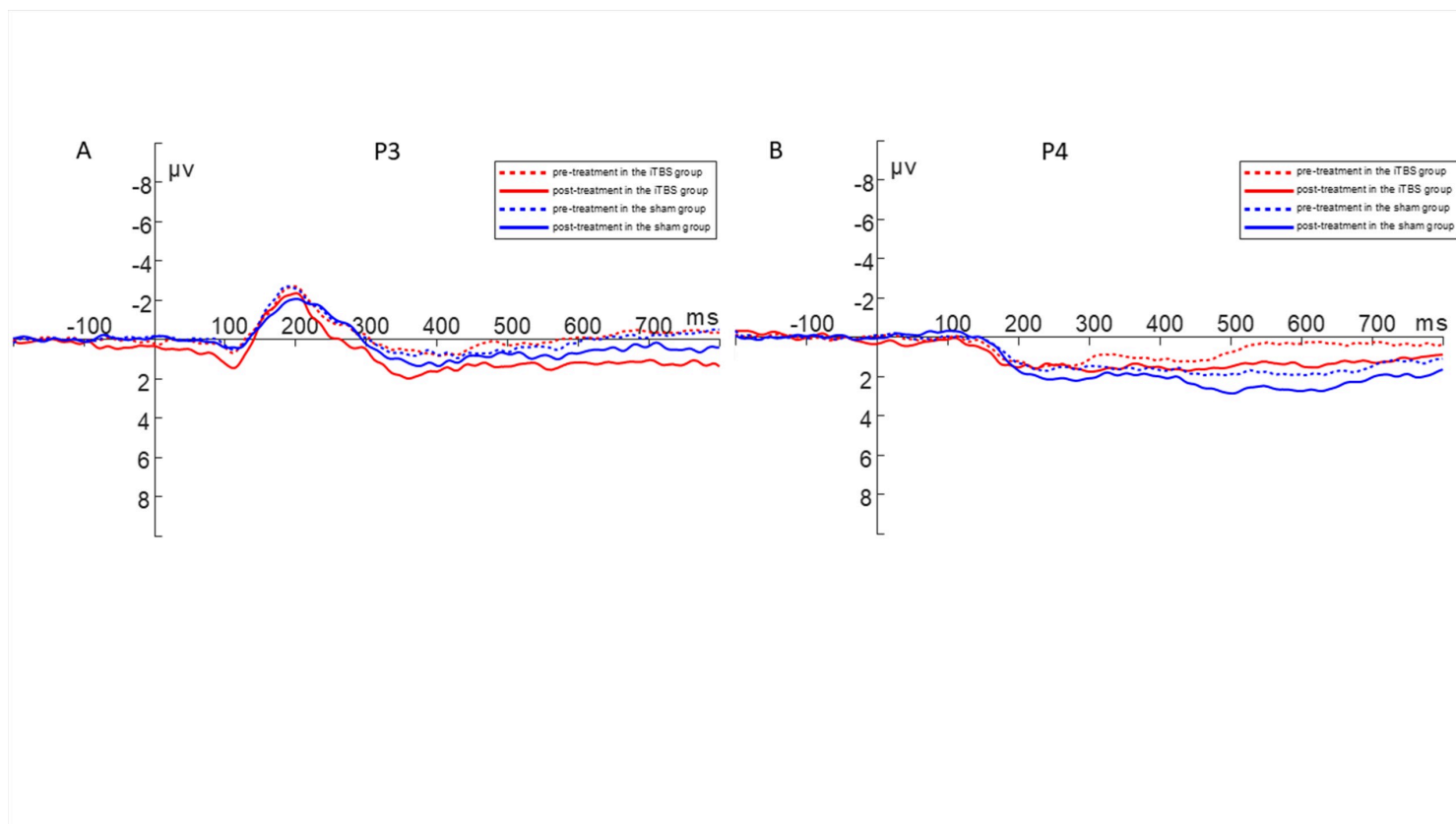


Figure 10

Comparison of grand-averaged P300 waveforms elicited by right valid cues before and after treatment in both groups.