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TMS-EEG Investigation of Cortical Activity Induced by Individualized rTMS in Patients with Prolonged Disorders of Consciousness

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Abstract

Objective: To establish an individualized repetitive transcranial magnetic stimulation (rTMS) target selection protocol based on resting-state electroencephalography (EEG) directed functional connectivity for patients with prolonged disorders of consciousness (pDoC), and to explore the underlying electrophysiological mechanisms using transcranial magnetic stimulation combined with EEG (TMS-EEG).

Methods: We enrolled 42 pDoC patients and randomly assigned to an individualized rTMS group, a conventional rTMS group, and a sham stimulation group. The individualized rTMS group selected the target with stronger directed functional connectivity between F3 and Pz as the stimulation site based on Granger causality analysis. The conventional rTMS group received random stimulation at either F3 or Pz. Both active groups received 10 sessions of high-frequency rTMS over 10 consecutive days, while the sham group underwent sham stimulation. Behavioral improvement and cortical connectivity were assessed before and after treatment using the Coma Recovery Scale-Revised (CRS-R) and TMS-EEG, respectively.

Results: CRS-R scores significantly increased in both the individualized and conventional rTMS groups ($p < 0.05$), whereas no significant improvement was observed in the sham group ($p > 0.05$). TMS-EEG analysis demonstrated that the amplitudes of N100 and P180 components significantly increased post-treatment in both active groups ($p < 0.05$), with no statistically significant changes in the sham group ($p > 0.05$). Global mean field amplitude (GMFA) significantly increased post-treatment in both active groups ($p < 0.05$). Specifically, significant increases were found in the 1-100 ms and 101-200 ms time windows post-treatment in both active groups ($p < 0.05$). Additionally, the individualized rTMS group showed a significant increase in the 201-300 ms window ($p < 0.05$), which was not observed in the conventional group ($p > 0.05$). No significant differences were found in the sham group across any time windows (1-100 ms, 101-200 ms, 201-300 ms, 301-400 ms, 401-500 ms; $p > 0.05$). Correlation analyses indicated that the change in CRS-R score positively correlated

with the change in N100 amplitude in both the individualized ($r = 0.82, p < 0.001$) and conventional ($r = 0.79, p = 0.001$) treatment groups. Similarly, the change in CRS-R score positively correlated with the change in P180 amplitude in the individualized ($r = 0.77, p = 0.0002$) and conventional ($r = 0.62, p = 0.025$) groups.

Conclusion: Individualized rTMS based on resting-state EEG directed functional connectivity is more effective in promoting consciousness recovery in pDoC patients. Compared to conventional rTMS, this approach may better facilitate the sustained propagation of post-stimulation cortical activity along residual consciousness networks and promote integration during middle-to-late stages. This study provides preliminary evidence supporting the transition of neuromodulation therapy for pDoC from fixed-target interventions to individualized precision regulation.

Trial registration: ClinicalTrials.gov, NCT05682248. **Ethics approval:** Ethics Committee of Xuanwu Hospital, 2022[022].

Keywords: Repetitive transcranial magnetic stimulation; Minimally conscious states; TMS-EEG; Coma Recovery Scale-Revised

1. Introduction

Prolonged disorders of consciousness (pDoC) are defined as a pathological state lasting over 28 days after severe brain injury affecting critical regions responsible for the initiation and maintenance of consciousness, including unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) [1, 2]. Given the severe deterioration in quality of life and the heavy socioeconomic burden, there is a critical imperative to establish more effective therapeutic strategies for pDoC [3, 4].

Effective clinical strategies for pDoC remain scarce. Repetitive transcranial magnetic stimulation (rTMS) shows considerable promise as a non-invasive neuromodulation technique. Xia et al. administered rTMS over the left dorsolateral prefrontal cortex (DLPFC) in 16 pDoC patients, reporting behavioral improvements in all 5 MCS patients and 4 out of 11 UWS patients[5]. Converging evidence suggests that rTMS modulates the internal milieu of patients, where preserved alpha power and rTMS-induced theta power suppression predict better treatment responsiveness[6]. Recent studies further indicate that rTMS targeting the left DLPFC improves behavioral outcomes in MCS, with pre-treatment PCIst scores accurately predicting clinical improvement[7]. Conversely, some studies have targeted the left primary motor cortex (M1) and observed enhanced peak systolic velocity and mean flow velocity in the left middle cerebral artery in MCS patients post-stimulation, whereas UWS/VS patients showed no significant hemodynamic changes[8]. Our research group previously conducted a series of studies applying rTMS over the posterior parietal cortex (PPC) in MCS patients[9-11]. Our findings demonstrate that PPC-rTMS dynamically modulates brain activity in some MCS patients, with such dynamic improvements correlating closely with consciousness recovery [11]. Current rTMS research for pDoC predominantly focuses on single-target interventions. Given the significant heterogeneity in lesion location and severity among pDoC, this one-size-fits-all approach fails to achieve truly personalized neuromodulation. Consequently, a key scientific challenge lies in transitioning the field from empirical practice to a precision

therapeutic paradigm guided by extracting individualized neural features, thereby enhancing treatment efficacy.

Prior studies have demonstrated that the therapeutic efficacy of transcranial direct current stimulation (tDCS) in pDoC is closely associated with the integrity of stimulated region and related residual functional networks [12, 13]. Specifically, tDCS responders showed preserved structural and metabolic integrity across key nodes of the consciousness network, such as the medial prefrontal cortex, posterior cingulate/precuneus, and thalamus, extending beyond the stimulated cortex[12]. Some studies suggest that rTMS enhances consciousness by modulating key cortical hubs and their connectivity with widespread networks, especially thalamocortical circuits, to drive trans-synaptic plasticity and the functional restoration of impaired networks[1, 14, 15]. This suggests that the efficacy of stimulation in targeting consciousness related networks hinges not merely on the anatomical accessibility of the site, but critically on the node's embedding within the preserved brain network and its information transmission capacity, thereby providing a theoretical basis for individualized treatment.

Recent advances in functional neuroimaging have shifted the paradigm of neuromodulation from isolated anatomical targets to mechanism-driven strategies based on brain network connectivity. Evidence suggests that the optimal site for intervention is determined by individual structural and functional connectivity, specifically the coupling between the target and critical pathological nodes, as well as its governing capacity within the whole brain network[16]. Complementary studies have proposed brain network models that characterize the brain as a complex system. Through graph-theoretic analysis or dynamic modeling, these approaches identify nodes with high network controllability or those located in regions of abnormal functional connectivity, thereby pinpointing stimulation sites most likely to drive global state transitions and shifting target selection from empirical to mechanistic decision-making[17]. Conversely, EEG provides a temporal complement by assessing brain states via functional connectivity and complexity metrics, thereby identifying prospective treatment responders and supporting real-time adaptive stimulation

strategies [7]. Accordingly, this study utilized resting-state EEG to map the residual consciousness network and compare frontal versus parietal targets of individual patients. By applying Granger Causality (GC) to quantify effective connectivity, we identified core driver hubs characterized by their superior capacity to govern information flow, which enables the optimized modulation of these networks. While transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) offers a novel technical approach for evaluating consciousness related brain network functions by directly measuring cortical excitability and effective connectivity [18, 19]. Through the analysis of causal brain responses to TMS, this technique characterizes the immediate reactivity, intensity, spatiotemporal dynamics, and network integration of the cortex.

In summary, this study aims to construct an individualized rTMS targeting protocol for pDoC patients based on EEG-derived directed functional connectivity. Furthermore, we will utilize TMS-EEG to elucidate the electrophysiological mechanisms underlying therapeutic efficacy.

2. Methods

2.1 Experimental design

All the pDoC patients were randomized into individualized rTMS, conventional rTMS, and sham control groups. Over 10 consecutive days, the individualized group received 10 Hz rTMS targeted to the parietal or prefrontal cortex based on effective connectivity, whereas the conventional and sham groups received active or sham stimulation applied randomly to these regions. All the eligible pDoC patients underwent clinical and TMS-EEG evaluation by blinded assessors at two time points: (1) before the first session of rTMS stimulation; (2) immediately after the 10 active sessions, as shown in figure 1.

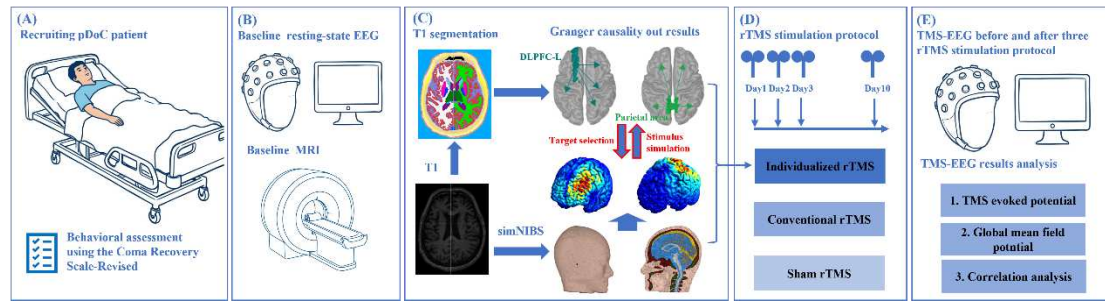


Figure 1. Experimental design.

2.2 Patients

We prospectively enrolled pDoC patients admitted to the Department of Rehabilitation Medicine at Xuanwu Hospital, Beijing, China, between February 2023 and January 2026. Inclusion criteria were: (1) a clinical diagnosis of UWS or MCS according to diagnostic criteria by CRS-R; (2) post-onset duration > 28 days; (3) age range 18-80 years; (4) etiologies including anoxia, trauma, or vascular events (hemorrhagic or ischemic); and (5) provision of written informed consent by a legal guardian. Exclusion criteria included: (1) pre-existing neurological disorders prior to coma; (2) concurrent therapies or pharmacological agents that modify cortical excitability; (3) presence of metallic intracranial implants, pacemakers, or neurostimulators within the target region; (4) comorbid epilepsy or excessive spontaneous movements; and (5) severe structural brain lesions at the stimulation site. During the experiment, all the patients continued to receive the basic rehabilitation program and medical care. The study was registered with ClinicalTrials.gov (NCT05682248) and was carried out according to the Declaration of Helsinki. The ethics approval was provided by the ethics committee of Xuanwu Hospital (approval number: 2022[022]).

2.3 Behavioral assessment

Behavioral assessment was performed using the CRS-R, a widely accepted instrument for evaluating the level of consciousness and neurobehavioral recovery in patients with pDoC [20]. After the clinical condition of each enrolled patient had stabilized, the CRS-R was administered in accordance with the standardized assessment protocol by two experienced rehabilitation physicians who were independent of the rTMS intervention and blinded to group allocation. The CRS-R comprises 23

hierarchically organized items across six subscales: auditory, visual, motor, oromotor/verbal, communication, and arousal functions. Assessments were conducted before and after treatment by the same two physicians to minimize inter-assessor variability and ensure consistency across time points.

2.4 Resting-state EEG and MRI for individualized stimulation target selection

2.4.1 EEG recordings and processing

EEG data were recorded using a 64-channel system (Brain Products GmbH, Germany) with sintered Ag/AgCl electrodes (EASYCAP GmbH, Germany) at a sampling rate of 2500 Hz. All recordings were performed at the bedside, with electrode impedances maintained below 5 k Ω . Each recording session was scheduled to last 10 min. If prolonged eye closure or electrographic signs of sleep occurred, data acquisition was suspended and the patient immediately received arousal stimulation of CRS-R assessment to maintain wakefulness. Data preprocessing was carried out in MATLAB (R2022a; MathWorks Inc., Natick, MA, USA) using the EEGLAB toolbox and comprised the following steps: (1) electrode localization; (2) removal of noisy epochs and interpolation of defective channels via spherical spline interpolation; (3) band-pass filtering (1–40 Hz); (4) downsampling to 250 Hz; (5) removal of ocular and muscular artifacts using independent component analysis (ICA); and (6) re-referencing to the common average across all channels.

2.4.2 EEG Source Reconstruction

In this study, individualized finite element method (FEM) head models comprising five tissue types-scalp, skull, cerebrospinal fluid, gray matter, and white matter-were constructed based on each subject's high-resolution T2-weighted structural magnetic resonance imaging (MRI) data using the Brainstorm software platform [21]. High-precision tetrahedral mesh models containing approximately 15,000 elements were generated to accurately characterize tissue conductivity properties. Based on these models, source reconstruction was performed using the Minimum Norm Estimate (MNE) combined with standardized Low-Resolution Brain Electromagnetic

Tomography (sLORETA) to map sensor-level electroencephalography (EEG) signals into the source space. Subsequently, the individual source space was co-registered to the MNI standard space via non-linear transformation, and the Automated Anatomical Labeling (AAL) atlas was applied to extract source time series for cortical nodes. Granger causality analysis was further employed to compute the directed effective connectivity strength between selected nodes (DLPFC-L, parietal area) and other brain nodes. The cortical nodes exhibiting significantly high out-degree identified as individualized modulation targets. These targets were then imported into the SimNIBS simulation platform, where the intracranial electric field distribution under transcranial stimulation was simulated using the individualized FEM head model (.msh mesh files) [22]. The physical validity of the targets was verified by evaluating the electric field intensity and direction within the target regions. Finally, the validated targets were transformed back into the MNI standard space to output precise coordinates, providing a spatial basis for subsequent neuronavigation-guided precise positioning and intervention.

2.4.3 Calculation of Granger causality

Granger causality analysis was performed to quantify directed functional connectivity between regions [23]. This approach is based on time-series predictability: if the inclusion of past values of $y(t)$ significantly improves the prediction of $x(t)$ beyond that achieved using the past values of $x(t)$ alone, y is considered to exert a directed predictive influence on x . Using a bivariate autoregressive model, with the two regional time series denoted as $x(t)$ and $y(t)$, the Granger causality from y to x was calculated as follows:

$$F_{y \rightarrow x} = \ln \left(\frac{\text{var}(\varepsilon_{(x|x)})}{\text{var}(\varepsilon_{(x|xy)})} \right)$$

Where, $\text{var}(\varepsilon_{x|x})$ represents the residual variance of the model in which $x(t)$ is predicted solely from its own past values, and $\text{var}(\varepsilon_{x|xy})$ represents the residual variance of the model in which $x(t)$ is predicted from the past values of both $x(t)$ and $y(t)$. Higher Granger causality values indicate a stronger directed predictive influence from y to x , and the statistical significance of this influence was evaluated using an F-test. Granger causality in the reverse direction, from x to y , was calculated analogously. All computations were performed using Brainstorm. The autoregressive model order was set to 10 based on the Akaike information criterion and Bayesian information criterion. The frequency resolution was set to 1 Hz, and the maximum frequency was restricted to 40 Hz to encompass the principal low-frequency EEG oscillations while minimizing potential contamination from electromyographic artifacts.

2.5 rTMS stimulation protocol

Stimulation intensity varied across this experiment, and was determined according to the resting motor threshold (RMT), identified as the minimum output intensity that induced a muscle contraction in which at least 5 out of 10 of the contractions had an amplitude $>50 \mu\text{V}$ peak-to-peak in the relaxed right abductor pollicis brevis.

For patients in the individualized rTMS group, directed functional connectivity between the candidate targets (parietal or prefrontal cortex) and other cortical sites, was estimated from resting EEG; the site exhibiting the greater out effective connectivity was chosen as the stimulation target. Patients in the conventional rTMS group and in the sham group were randomly assigned the parietal or prefrontal cortex as the target in a 1:1 ratio. TMS pulses were delivered via a Magstim Rapid² stimulator with a 70 mm figure-of-eight coil (Magstim Company Limited, Whitland, UK) placed tangentially onto the scalp over the target cortex. An EEG cap marked with the International 10-20 EEG System was used to identify the Pz (the parietal area) and the F3 (the prefrontal area) stimulation site. Daily intervention sessions consisted of 1,000 pulses (10 Hz) at an intensity of 90% RMT. The stimulation of one session included 10 trains, with each train lasting 10 s with a 30 s inter-train pause. The rise time of the magnetic monophasic stimulus was approximately 100 μs and time to zero was approximately 800 μs . The sham group used identical parameter settings but with the

coil positioned perpendicular (90°) to the target and one coil edge lightly touching the scalp so that effective intracranial stimulation was essentially zero.

2.6 TMS-EEG for measuring rTMS modulation effects

2.6.1 TMS-EEG Procedures

TMS-EEG data were acquired using MR-compatible BrainAmp amplifiers and 64 MR-compatible electrodes (Brain Products GmbH, Germany) at a sampling rate of 2,500 Hz. Single-pulse TMS was delivered using a Magstim Rapid² stimulator connected to a 70-mm air-cooled figure-of-eight coil (Magstim Company Limited, Whitland, UK). Electrode impedances were maintained below 5 k Ω throughout data acquisition. To attenuate the bone-conducted transmission of the TMS coil-click sound and thereby minimize TMS-evoked auditory responses, a thin layer of foam was placed between the coil and the scalp. The RMT was determined as described in Section 2.3, and the stimulation intensity was set at 90% of the RMT to reduce stimulation-related electromyographic contamination. Based on previous studies, the left DLPFC, corresponding to the F3 electrode position in the International 10-20 EEG system, was selected as the stimulation site. The coil was positioned tangentially to the scalp over F3, with its handle oriented at approximately 45° relative to the sagittal midline. Each TMS-EEG session comprised 150 single-pulse trials delivered with randomly jittered interstimulus intervals ranging from 2.1 to 3.1 s.

2.6.2 TMS-EEG pre-process

TMS-EEG data were preprocessed in MATLAB (R2022a; MathWorks Inc., Natick, MA, USA) using the EEGLAB and TESA[24] toolbox as the following steps: (1) detection and marking of TMS pulses, followed by segmentation of the continuous EEG data into epochs extending from 1,000 ms before and after each TMS pulse.; (2) visual inspection and rejection of epochs contaminated by excessive noise, ocular artifacts, or muscular activity; (3) downsampling of the retained epochs to 1,000 Hz, bandpass (1-80 Hz) and bandstop (48-52 Hz) filtering using Butterworth filter; (4) removal of residual TMS-related, ocular, and muscular artifacts using independent component analysis (ICA); (5) baseline correction using the pre-stimulus interval; and (6) re-

referencing of the cleaned data to the common average across all channels. A total of 60 independent components (ICs) were extracted for each dataset. Artifact-related ICs were identified by visual inspection of their scalp topographies, trial-by-trial activation patterns, averaged evoked responses, power spectra, and component time series, and were subsequently removed.

2.6.3 TMS-EEG data feature analysis

TMS-evoked potentials (TEPs) were evaluated in the time domain using butterfly plots, and global mean field amplitude (GMFA) was calculated to characterize the temporal variation in response magnitude across all electrodes. The amplitudes and latencies of the P30, N45, P60, N100, and P180 components were extracted. At each time point, GMFA was calculated as the spatial standard deviation of the voltage distribution across electrodes according to the following equation:

$$GMFA(t) = \sqrt{\left[\frac{\sum_i^k (V_i(t) - V_{mean}(t))^2}{k} \right]}$$

Where, k represents the total number of electrodes, V_i represents the voltage recorded at electrode i , V_{mean} represents the average voltages of all electrodes.

2.7 Statistical analysis

The data were analyzed using SPSS version 26.0 (SPSS, Chicago, IL). Continuous variables are presented as mean $\pm$ standard deviation ($M \pm SD$), and categorical variables as counts (percentages). The significance level was set at $\alpha = 0.05$, and all reported p -values are two-sided.

2.7.1 Comparison of clinical demographic data

Continuous variables (age, disease course): Between-group comparisons were performed using the Kruskal-Wallis test (chosen due to the small sample size and its independence from the normality assumption), with the H -statistic and p -value reported. Categorical variables (gender, diagnosis, etiology, stimulation target): Comparisons were made using the Pearson chi-square test (or Fisher's exact test when expected frequencies were <5), and Cramer's V was calculated as a measure of effect size. Significance levels are denoted as: * $p < 0.05$, ** $p < 0.01$.

2.7.2 Comparison of CRS-R value and EEG features

Within-group comparisons: For each EEG feature (CRS-R, N100, P180, GMFA), paired-samples t-tests were conducted separately within each group (I, C, and S) to compare pre- and post-treatment values. Cohen's *d* effect sizes and their 95% confidence intervals were calculated.

Multivariate analysis: For each feature, a 3 (Group: individualized, conventional and sham) $\times$ 2 (Time: pre, post) mixed-design repeated-measures analysis of variance (ANOVA) was performed, with Group as the between-subjects factor and Time as the within-subjects factor. For each effect, the *F*-value, degrees of freedom, partial eta-squared (η^2), and *p*-value are reported. Since the Time factor had only two levels, the sphericity assumption was automatically satisfied, and no Greenhouse-Geisser correction was required.

3. Results

3.1 Clinical demographic data

This study enrolled patients into three groups: the individualized treatment group (Group I), the conventional treatment group (Group C), and the sham stimulation group (Group S). All patients' clinical information is shown in Table 1. Supplementary Table 2 presents the Granger causality connectivity results for patients in Group I. Baseline assessments demonstrated well-balanced and comparable clinical and demographic characteristics across the three groups. Specifically, no statistically significant differences were observed among the groups in terms of age, disease duration, gender distribution, clinical diagnosis (MCS versus UWS), etiology (hemorrhagic, ischemic, and traumatic brain injuries), or stimulation targets (F3 and Pz). Regarding age, Groups I and C were 58.4 ± 13.3 years, and Group S was 57.4 ± 14.0 years (Kruskal-Wallis test, $H = 0.941$, $p > 0.05$). The disease durations were 4.9 ± 2.5 months, 4.9 ± 2.5 months, and 4.1 ± 2.4 months, respectively ($H = 0.625$, $p > 0.05$). In terms of gender distribution, Groups I and C comprised 9 males and 5 females, whereas Group S comprised 11 males and 3 females ($\chi^2 = 0.891$, $df = 2$, $p = 0.640$, Cramer's $V = 0.146$). The diagnostic composition was identical across all groups, with each containing 11 MCS patients and

3 UWS patients ($\chi^2 = 0.000$, $p = 1.000$). Furthermore, the distribution of etiologies, including hemorrhagic, ischemic, and traumatic brain injuries, showed no significant intergroup differences ($\chi^2 = 3.091$, $df = 4$, $p = 0.543$, Cramer's $V = 0.192$). Additionally, the allocation of stimulation targets (F3 and Pz) was perfectly matched across all groups, with exactly 7 patients assigned to each target ($\chi^2 = 0.000$, $p = 1.000$).

3.2 CRS-R

A two-way repeated-measures analysis of variance (ANOVA) on the Coma Recovery Scale-Revised (CRS-R) scores revealed a significant main effect of time ($F(1, 39) = 69.42$, $p < 0.001$, $\eta^2 = 0.640$) and a non-significant main effect of group ($F(2, 39) = 0.17$, $p = 0.845$); however, the significant group-by-time interaction ($F(2, 39) = 15.13$, $p < 0.001$, $\eta^2 = 0.437$) indicated that the trajectories of improvement over time differed significantly among the groups. Subsequent simple effect analyses using paired t-tests demonstrated that the Group I exhibited a significant increase in post-treatment scores (11.93 ± 4.16) compared to pre-treatment baseline (9.36 ± 3.77 ; $t(13) = 6.19$, $p < 0.001$, Cohen's $d = 1.65$). Similarly, the Group C showed significant improvement from pre-treatment (9.21 ± 3.14) to post-treatment (10.43 ± 3.20 ; $t(13) = 5.67$, $p < 0.001$, Cohen's $d = 1.51$). In contrast, the Group S did not demonstrate a statistically significant change between pre-treatment (10.07 ± 4.05) and post-treatment (10.43 ± 4.16) assessments ($t(13) = 2.11$, $p = 0.055$), as shown in Supplementary Table 2 and Figure 2.

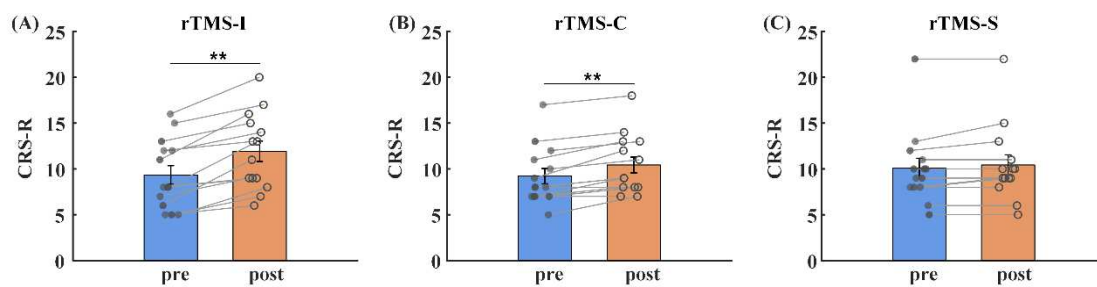


Figure 2. CRS-R values for individualized rTMS group, conventional rTMS group and sham group.

3.2 TEPs

Butterfly plots of TEPs revealed more widespread and robust EEG responses to TMS across channels post-rTMS compared to baseline in individualized and conventional rTMS groups, while the sham group showed similar response patterns before and after treatment (Figure 3).

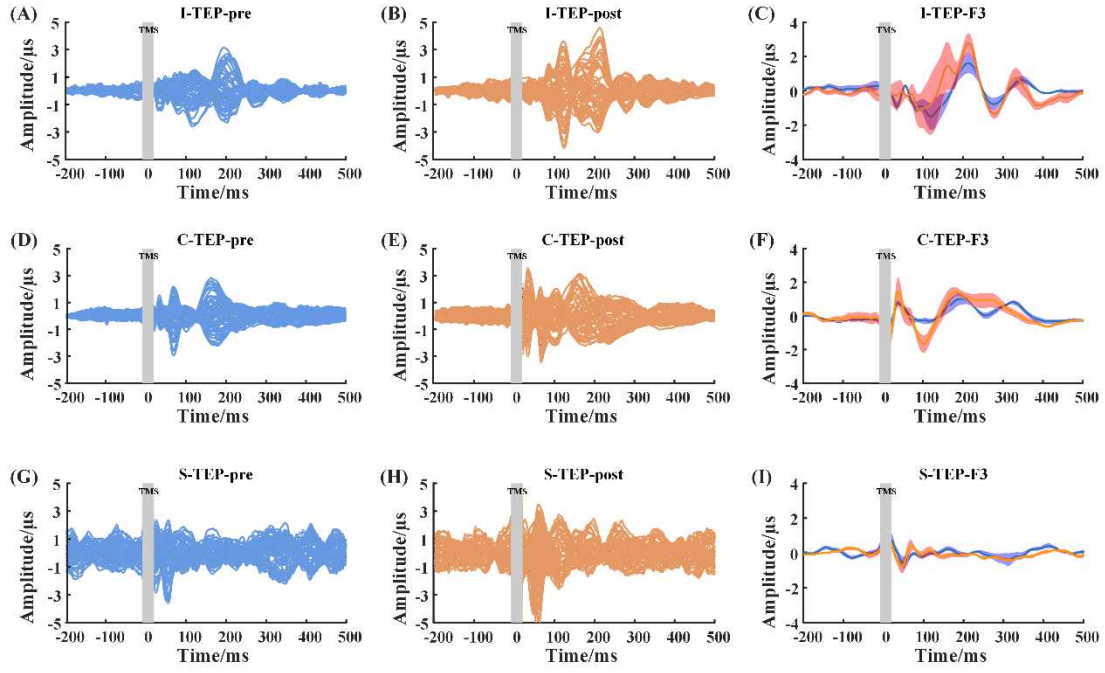


Figure 3. Butterfly plots of TEPs for individualized rTMS group, conventional rTMS group and sham group.

(A-F) Butterfly plots of TEPs before (left column: A, C, E) and after (right column: B, D, F) rTMS. (A, B) Individualized rTMS group; (C, D) Conventional rTMS group; (E, F) Sham group. (G-I) Butterfly plots of the F3 electrode for the (G) individualized rTMS group, (H) conventional rTMS group, and (I) sham group, respectively. Blue lines represent pre-rTMS data, while red lines indicate post-rTMS data. The solid line represents the mean TEP and the shaded area represents the mean $\pm$ standard deviation (STD).

A two-way repeated-measures analysis of variance (ANOVA) on the N100 amplitudes revealed a significant main effect of time ($F(1, 39) = 53.09, p < 0.001, \eta_p^2 = 0.577$) and a non-significant main effect of group ($F(2, 39) = 0.86, p = 0.432$). Notably, the group-by-time interaction was highly significant ($F(2, 39) = 29.21, p < 0.001, \eta_p^2 = 0.600$), indicating substantial differences in the pre- and post-intervention trajectories across the groups. Subsequent simple effect analyses using paired t -tests demonstrated that the conventional treatment group (Group C) exhibited a highly significant increase in N100 amplitude post-treatment (0.81 ± 0.36) compared to the pre-treatment baseline (0.17 ± 0.15 ; $t(13) = 7.45, p < 0.001$, Cohen's $d = 1.99$). Similarly, the individualized treatment group (Group I) showed significant improvement from pre-treatment (0.27 ± 0.32) to post-treatment (0.44 ± 0.49 ; $t(13) = 2.79, p = 0.015$, Cohen's $d = 0.75$). In contrast, the sham stimulation group (Group S) did not demonstrate a statistically

significant change between pre-treatment (0.54 ± 0.46) and post-treatment (0.52 ± 0.42) assessments ($t(13) = -0.71, p = 0.491$).

A two-way repeated-measures analysis of variance (ANOVA) on the P180 amplitudes revealed significant main effects of both group ($F(2, 39) = 14.36, p < 0.001, \eta_p^2 = 0.424$) and time ($F(1, 39) = 40.24, p < 0.001, \eta_p^2 = 0.508$). Furthermore, the group-by-time interaction was highly significant ($F(2, 39) = 10.67, p < 0.001, \eta_p^2 = 0.354$), indicating substantial differences in the pre- and post-intervention trajectories across the groups. Subsequent simple effect analyses using paired t -tests demonstrated that the individualized treatment group (Group I) exhibited a highly significant increase in P180 amplitude post-treatment (1.07 ± 0.11) compared to the pre-treatment baseline (0.84 ± 0.16 ; $t(13) = 6.46, p < 0.001$, Cohen's $d = 1.73$). Similarly, the conventional treatment group (Group C) showed significant improvement from pre-treatment (0.33 ± 0.20) to post-treatment (0.68 ± 0.34 ; $t(13) = 4.69, p < 0.001$, Cohen's $d = 1.25$). In contrast, the sham stimulation group (Group S) did not demonstrate a statistically significant change between pre-treatment (0.48 ± 0.37) and post-treatment (0.48 ± 0.38) assessments ($t(13) = 0.14, p = 0.889$). The results are shown in Supplementary Tables 3 and 4 and Figure 4.

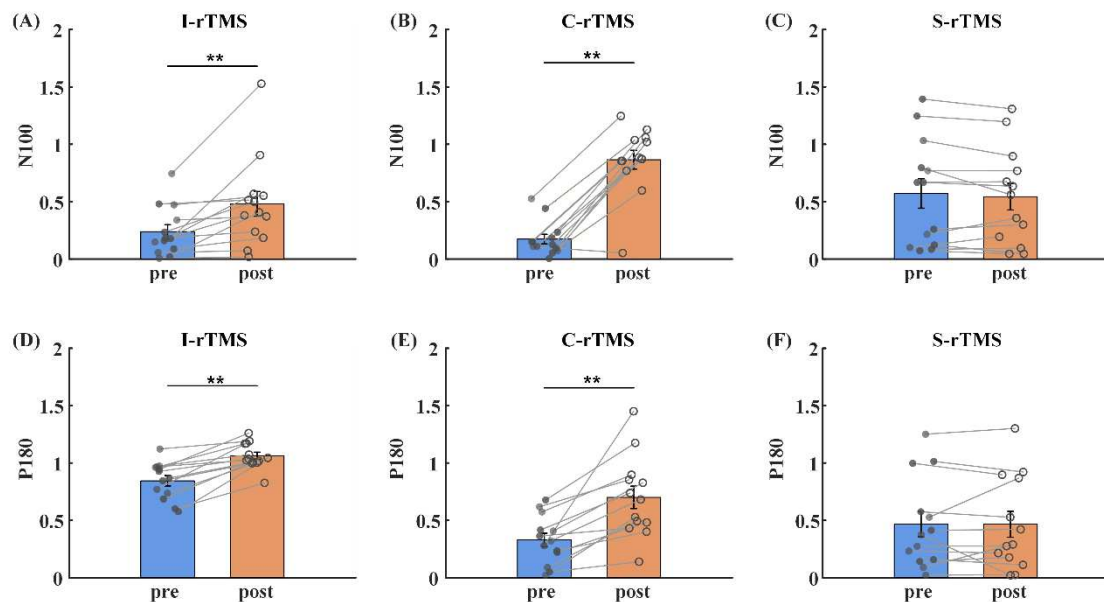


Figure 4. N100 and P180 results for individualized rTMS group, conventional rTMS group and sham group.

(A-C) N100 results pre- (left columns) and post- (right columns) rTMS. (A) Individualized rTMS group; (B) Conventional rTMS group; (C) Sham group. (D-F) P180 results pre- (left columns) and

post- (right columns) rTMS. (D) Individualized rTMS group; (E) Conventional rTMS group; (F) Sham group. * indicates $p < 0.05$.

3.3 GMFA

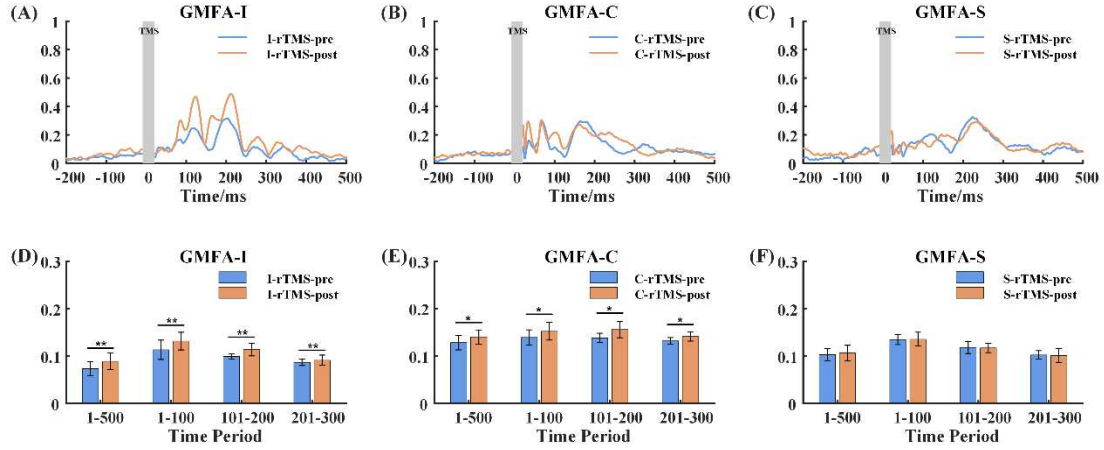


Figure 5. GMFA results pre- and post- rTMS for individualized rTMS group, conventional rTMS group and sham group.

(A-C) GMFA results pre- (blue lines) and post- (orange lines) rTMS. (A) Individualized rTMS group; (B) Conventional rTMS group; (C) Sham group. (D-F) GMFA results pre- (blue columns) and post- (orange columns) rTMS in time windows of 1-500ms, 1-100ms, 101-200ms and 201-300ms. (D) Individualized rTMS group; (E) Conventional rTMS group; (F) Sham group. * indicates $p < 0.05$.

A two-way repeated-measures analysis of variance (ANOVA) on the GMFA in time windows of 1-500ms revealed significant main effects of both group ($F(2, 39) = 9.23, p < 0.001, \eta_p^2 = 0.321$) and time ($F(1, 39) = 49.17, p < 0.001, \eta_p^2 = 0.558$). Furthermore, the group-by-time interaction was highly significant ($F(2, 39) = 10.63, p < 0.001, \eta_p^2 = 0.353$), indicating substantial differences in the pre- and post-intervention trajectories across the groups. Subsequent simple effect analyses using paired t -tests demonstrated that the individualized treatment group (Group I) exhibited a highly significant increase in GMFA1 amplitude post-treatment (0.089 ± 0.047) compared to the pre-treatment baseline (0.033 ± 0.017 ; $t(13) = 5.35, p < 0.001$, Cohen's $d = 1.43$). Similarly, the conventional treatment group (Group C) showed significant improvement from pre-treatment (0.089 ± 0.033) to post-treatment (0.143 ± 0.048 ; $t(13) = 4.71, p < 0.001$, Cohen's $d = 1.26$). In contrast, the sham stimulation group (Group S) did not demonstrate a statistically significant change between pre-treatment

(0.108 ± 0.047) and post-treatment (0.111 ± 0.044) assessments ($t(13) = 0.65, p = 0.529$).

Furthermore, both the individualized and conventional rTMS groups exhibited a significant increase in time windows of 1-100ms, 101-200ms ($p < 0.001$), whereas no significant changes were observed in the sham group ($p > 0.05$). In the 201-300 ms window, this significant increase persisted only in the individualized rTMS group ($p = 0.046$). The results are shown in Supplementary Table 5 and Figure 5.

3.4 Correlation results between TEPs changes and CRS-R scores changes

Correlation analysis showed that in the individualized rTMS group, N100 changes were significantly correlated with CRS-R changes both before ($r = 0.82, p < 0.001$) and after ($r = 0.79, p = 0.001$) treatment. Similarly, in the conventional rTMS group, significant correlations were observed between P180 changes and CRS-R changes before ($r = 0.77, p < 0.001$) and after ($r = 0.62, p = 0.025$) treatment.

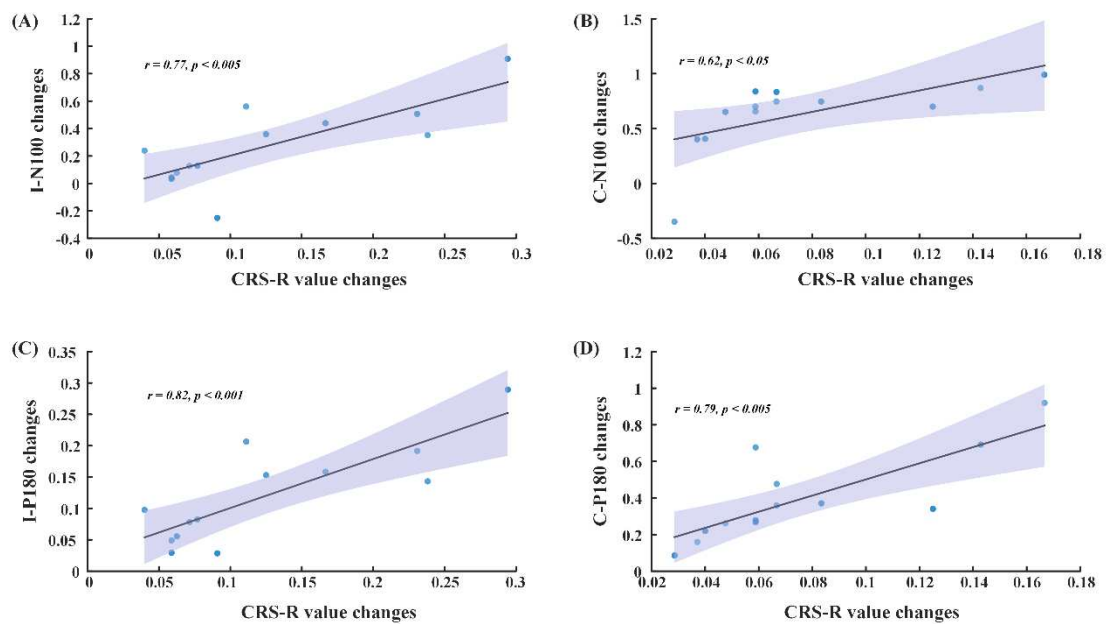


Figure 6. Correlation between TEPs changes and CRS-R scores changes before and after rTMS for individualized rTMS group and conventional rTMS group.

Correlation results between TEPs changes and CRS-R scores changes before and after rTMS. Correlations between N100 and CRS-R score changes before and after treatment in the individualized (A) and conventional (B) rTMS group. Correlations between P180 and CRS-R score changes before and after treatment in the individualized (C) and conventional (D) rTMS group.

4. Discussion

Individualized rTMS Improves Brain Activity in DOC

This study utilized TMS-EEG technology to measure cortical reactivity and compared the differences in neural activity among the individualized treatment group, the conventional treatment group, and the sham stimulation group. The results showed that the global mean field amplitude (GMFA) in the overall 1-500 ms post-stimulus time window was significantly higher after treatment in both the individualized and conventional treatment groups compared to their pre-treatment baseline, with significant enhancements observed in both the 1-100 ms and 101-200 ms time windows, whereas no significant changes were observed in the sham stimulation group. These findings suggest that individualized rTMS can enhance cortical excitability and connectivity in DOC. Further analysis revealed that within the 201-300 ms time window, only the individualized treatment group exhibited a statistically significant increase in post-treatment GMFA compared to pre-treatment, whereas the conventional treatment group showed an upward trend that did not reach statistical significance. Considering that the neurophysiological processes reflected in this time window are no longer confined to immediate local cortical responses to stimulation, but rather involve the sustained propagation of stimulation effects to distant brain regions and network-level integration[25, 26], the advantages of the individualized treatment protocol may not primarily manifest as enhanced local stimulation effects. Instead, they may be more closely related to improved sustained propagation and integration capabilities of post-stimulus activity within residual consciousness networks[25]. The present study demonstrated that only the individualized treatment group achieved a statistically significant increase in post-treatment GMFA within this time window, whereas the conventional treatment group merely showed a non-significant upward trend. Generally, the 1-100 ms window is considered to reflect early responses of the local and adjacent cortex to stimulation, whereas responses after 200 ms are more likely to involve the sustained propagation of post-stimulus activity to distant brain regions and network-level integration[26]. Rosanova et al. indicated that patients with better states of

consciousness are more likely to exhibit sustained and spatially complex TMS-evoked responses extending to distant regions, whereas those with poorer states of consciousness predominantly show localized and transient responses[27]. Therefore, the preserved enhancement observed in the individualized treatment group within the 201-300 ms time window suggests that this approach may better facilitate the sustained propagation of post-stimulus activity along residual consciousness networks and promote mid-to-late stage integration. This may serve as an important neurophysiological basis for its superior behavioral efficacy compared to the conventional treatment group.

Furthermore, existing fixed-parameter rTMS protocols, particularly those with fixed targets, can improve cortical activity and promote consciousness recovery in DOC, with the prefrontal and parietal cortices identified as critical targets for neuromodulation. Previous rTMS studies have confirmed that modulating neural activity in the frontal and parietal lobes can improve conscious activity in DOC patients. However, the therapeutic effects remain limited. Consequently, individualized parameter settings for rTMS have emerged as a crucial approach to enhancing modulation efficacy. An experimental study on individualized rTMS based on brain function assessment in DOC selected stimulation targets according to individual-level brain network abnormalities, including frontal and parietal targets. The design rationale of this study aligns with the present research, providing important evidence for individualized neuromodulation techniques in DOC [28]. Steven et al. proposed an individualized neuromodulation protocol for DOC based on brain state assessment, encompassing various modulation techniques and further expanding the scope of individualized interventions [4]. Recent studies in the psychiatric field have begun to incorporate individualized rTMS protocols that combine individual functional connectivity, demonstrating that individualized rTMS can improve brain network characteristics in subjects [29]. In light of these findings, the present study utilized brain network analysis results in DOC, specifically directed connectivity within the frontoparietal network, to guide individualized rTMS target selection. By employing Granger Causality (GC) analysis, we precisely characterized the directionality and

hierarchical structure of information flow within the frontoparietal network, thereby identifying core hubs with true "driving effects" (either frontal or parietal) to achieve optimized modulation of residual frontoparietal consciousness networks. As the core architecture of the brain's "global workspace," the Frontoparietal Network (FPN) plays critical roles in information integration and cognitive control [30]. The integrity and dynamic reorganization capacity of its functional connectivity are decisive factors for consciousness recovery in DOC patients [31, 32]. A foundational mechanistic study established the central role of the FPN in distinguishing conscious from unconscious states, demonstrating that complex spatiotemporal signal coordination patterns are primarily concentrated in the frontoparietal region, thus providing a theoretical cornerstone for recovering consciousness through neuromodulation targeting this network[33]. Additionally, dynamic functional connectivity analysis has revealed that consciousness recovery relies not merely on static increases in connection strength, but on the dwell time of the brain in "highly integrated frontoparietal states." The FPN serves as a key biomarker for predicting consciousness recovery, further supporting the necessity of targeting this network[31, 34]. Neuromodulation targeting the FPN can effectively induce global functional connectivity remodeling, particularly by enhancing long-range synchronization within the FPN and between the thalamocortical system, thereby significantly improving consciousness levels [3, 35]. Clinical evidence confirms that significant improvements in patients' consciousness levels (CRS-R scores) are closely correlated with increased FPN connectivity strength [13]. Exploring and implementing this translational pathway will provide urgently needed theoretical guidance for the individualized treatment of disorders of consciousness.

Individualized rTMS Improves Cortical Activity to Promote Consciousness Recovery

This study reports that individualized rTMS can enhance cortical excitability in patients with DOC, and these improvements in cortical activity are closely associated with behavioral enhancements in consciousness levels. The central thalamic theory of consciousness posits that the disruption of the prefrontal-thalamic circuit is a critical mechanism underlying the loss of consciousness [14]. Given the mapping relationship

between the cortex and the thalamus, improvements in cortical activity can reflect the restoration of the thalamocortical circuit[36], thereby elucidating how enhanced cortical activity facilitates consciousness recovery [37, 38]. Existing neuromodulation studies in DOC have reported that increased cortical excitability is closely linked to conscious behavior. Furthermore, the Global Neuronal Workspace (GNW) theory [39] and the Information Integration Theory (IIT)[40] are currently prominent theories of consciousness that explain DOC recovery through cortical activity. The GNW theory posits that the frontal lobe's processing and broadcasting of external information to the entire brain is critical for conscious awareness, whereas IIT suggests that the parietal lobe processes external stimuli and achieves whole-brain integration and differentiation to form consciousness [41]. Both theories emphasize the pivotal role of these two brain regions in consciousness formation, while concurrently asserting that cortical information processing is essential for conscious awareness. Our findings corroborate, from the perspectives of both theories, that individualized rTMS-induced improvements in cortical activity facilitate consciousness recovery in DOC. Furthermore, the results further suggest that DOC neuromodulation therapy relies on the reconstruction of residual brain networks [42, 43]. The central thalamic theory proposes that impaired corticocortical and corticothalamic information transmission leads to diminished integration capacity of consciousness-related networks [44, 45]. The therapeutic effects of rTMS are not confined to the local stimulation site but may depend on the stimulation target's participation in restoring information propagation within residual brain networks, thereby influencing broader consciousness-related circuits [4, 27]. Therefore, when choosing between two candidate targets with theoretical support, prioritizing the target with stronger effective functional connectivity may imply selecting a stimulation site with relatively higher propagation potential within the patient's residual consciousness network. This strategy may enhance the likelihood of stimulation effects acting upon residual consciousness networks and further amplify the modulatory effects on large-scale brain networks.

5. Conclusion

Individualized rTMS based on resting-state EEG directed functional connectivity is more effective in promoting consciousness recovery in pDoC patients. Compared to conventional rTMS, this approach may better facilitate the sustained propagation of post-stimulation cortical activity along residual consciousness networks and promote integration during middle-to-late stages. This study provides preliminary evidence supporting the transition of neuromodulation therapy for pDoC from fixed-target interventions to individualized precision regulation.

6. Declarations

Ethics approval and consent to participate

The study was registered with ClinicalTrials.gov (NCT05682248) and was carried out according to the Declaration of Helsinki. The ethics approval was provided by the ethics committee of Xuanwu Hospital (approval number: 2022[022]). Written informed consent was obtained from the patients' families or legal representatives.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials in the study are available upon reasonable request to the authors.

Competing interests

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

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Authors' contributions

Y.Z.: funding support, visualization, data collection and original draft writing. X.Y. and Z.Z.: data collection and visualization. J.D.: prognostic follow-up. L.C.: data collection and visualization. W.S.: funding support, review-editing and data review. Y.W.: methodology, review of data analysis and manuscript. All authors reviewed the manuscript.

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Table 1. General conditions of pDoC patients.

	Gender	Age (years)	Diagnosis	Course (months)	Etiology	Stimulation target	CRS-R of baseline	CRS-R of baseline
Individualized rTMS group								
P1	M	35	MCS	7	Hemorrhagic	Pz	6 (0-3-0-1-0-2)	11 (3-3-2-1-0-2)
P2	M	71	MCS	7	Traumatic	Pz	8 (0-1-4-1-0-2)	9 (0-1-5-1-0-2)
P3	F	70	MCS	10	Hemorrhagic	Pz	12 (2-1-5-2-0-2)	14 (2-3-5-2-0-2)
P4	M	59	MCS	8	Hemorrhagic	Pz	8 (0-0-4-2-0-2)	9 (0-0-5-2-0-2)
P5	M	67	MCS	6	Hemorrhagic	Pz	15 (3-3-3-2-1-3)	17 (3-3-5-2-1-3)
P6	F	69	MCS	4	Hemorrhagic	Pz	16 (3-3-5-2-0-3)	20 (4-4-6-2-1-3)
P7	M	63	MCS	5	Ischemic	Pz	13 (2-3-5-1-0-2)	15 (2-3-5-2-0-3)
P8	M	36	UWS	2	Traumatic	F3	5 (0-1-1-1-0-2)	8 (1-3-1-1-0-2)
P9	F	65	MCS	2	Hemorrhagic	F3	7 (0-2-2-1-0-2)	9 (1-3-2-1-0-2)
P10	M	58	MCS	3	Hemorrhagic	F3	5 (0-1-1-1-0-2)	6 (1-2-1-1-0-2)
P11	F	69	UWS	4	Hemorrhagic	F3	12 (2-3-3-1-0-3)	13 (2-3-4-1-0-3)
P12	M	66	MCS	2	Traumatic	F3	5 (1-1-2-0-0-1)	7 (1-2-2-0-0-2)
P13	F	53	UWS	6	Hemorrhagic	F3	11 (2-3-2-1-0-3)	16 (3-4-4-1-1-3)
P14	M	36	MCS	3	Traumatic	F3	8 (1-3-1-1-0-2)	13 (2-3-4-1-0-3)

Conventional rTMS group

P1	F	63	MCS	7	Hemorrhagic	Pz	10 (2-2-2-1-0-3)	11 (2-3-2-1-0-3)
P2	M	46	UWS	3	Traumatic	Pz	7 (1-1-2-1-0-2)	9 (2-2-2-1-0-2)
P3	M	64	MCS	5	Hemorrhagic	Pz	13 (1-3-4-2-0-3)	14 (2-3-4-2-0-3)
P4	F	76	MCS	1	Hemorrhagic	Pz	11 (2-3-3-0-0-3)	13 (3-3-4-0-0-3)
P5	F	48	UWS	3	HIE	Pz	7 (1-1-2-1-0-2)	7 (1-1-2-1-0-2)
P6	F	63	MCS	12	Traumatic	Pz	17 (3-4-5-2-0-3)	18 (3-4-5-2-1-3)
P7	M	47	MCS	8	Hemorrhagic	Pz	7 (1-3-1-0-0-2)	8 (1-4-1-0-0-2)
P8	M	32	MCS	5	Traumatic	F3	12 (2-3-5-0-0-2)	13 (2-3-5-1-0-2)
P9	F	56	MCS	5	Traumatic	F3	8 (1-0-3-2-0-2)	8 (1-0-3-2-0-2)
P10	F	53	MCS	2	Hemorrhagic	F3	9 (1-2-3-1-0-2)	12 (1-3-4-2-0-2)
P11	M	54	MCS	3	Traumatic	F3	5 (0-2-0-1-0-2)	7 (1-2-1-1-0-2)
P12	F	65	MCS	3	Hemorrhagic	F3	8 (1-2-2-1-0-2)	9 (1-3-2-1-0-2)
P13	M	28	MCS	5	Traumatic	F3	8 (1-2-2-1-0-2)	9 (1-3-2-1-0-2)
P14	F	58	UWS	9	Hemorrhagic	F3	7 (1-1-2-1-0-2)	8 (1-2-2-1-0-2)

Sham stimulation group

P1	M	51	MCS	3	Traumatic	Pz	11 (1-2-5-1-0-2)	11 (1-2-5-1-0-2)
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P2	M	32	MCS	5	Traumatic	Pz	12 (2-3-5-0-0-2)	13 (2-3-5-1-0-2)
P3	M	71	MCS	7	Traumatic	Pz	9 (0-1-5-1-0-2)	9 (0-1-5-1-0-2)
P4	F	56	MCS	5	Traumatic	Pz	8 (1-0-3-2-0-2)	8 (1-0-3-2-0-2)
P5	M	55	MCS	5	Hemorrhagic	Pz	10 (2-3-2-1-0-2)	10 (2-3-2-1-0-2)
P6	M	54	UWS	2	Traumatic	Pz	5 (0-2-0-1-0-2)	5 (0-2-0-1-0-2)
P7	M	65	MCS	1	Hemorrhagic	Pz	13 (3-3-3-2-0-2)	15 (3-3-5-2-0-2)
P8	F	70	MCS	10	Hemorrhagic	F3	10 (0-1-5-2-0-2)	10 (0-1-5-2-0-2)
P9	M	72	MCS	3	Ischemic	F3	10 (1-3-2-1-0-3)	10 (1-3-2-1-0-3)
P10	M	63	MCS	4	Hemorrhagic	F3	8 (2-1-2-1-0-2)	9 (2-2-2-1-0-2)
P11	M	58	UWS	3	Hemorrhagic	F3	6 (1-1-1-1-0-2)	6 (1-1-1-1-0-2)
P12	M	28	UWS	5	Traumatic	F3	9 (1-3-2-1-0-2)	9 (1-3-2-1-0-2)
P13	M	75	MCS	1	Ischemic	F3	22 (4-5-6-2-2-3)	22 (4-5-6-2-2-3)
P14	F	54	MCS	4	Traumatic	F3	8 (2-2-1-1-0-2)	9 (2-3-1-1-0-2)

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