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Research article

Effects of parietal repetitive transcranial magnetic stimulation in prolonged disorders of consciousness: A pilot study

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ABSTRACT

Objective: Although the parietal cortex is related to consciousness, the dorsolateral prefrontal and primary motor cortices are the usual targets for repetitive transcranial magnetic stimulation (rTMS) for prolonged disorders of consciousness (pDoC). Herein, we applied parietal rTMS to patients with pDoC, to verify its neurobehavioral effects and explore a new potential rTMS target.
Materials and methods: Twenty-six patients with pDoC were assigned to a rTMS or sham group. The rTMS group received 10 sessions of parietal rTMS; the sham group received 10 sessions of sham stimulation. The Coma Recovery Scale-Revised (CRS-R) and event-related potential (ERP) were collected before and after the 10 sessions or sham sessions.
Results: After the 10 sessions, the rTMS group showed: a significant CRS-R score increase; ERP appearance of a P300 waveform and significantly increased Fz amplitudes; increased potentials on topographic mapping, especially in the left prefrontal cortex; and an increase in delta and theta band powers at Fz, Cz, and Pz. The sham group did not show such changes in CRS-R score or ERP results statistically.
Conclusion: Parietal rTMS shows promise as a novel intervention in the recovery of consciousness in pDoC. It showed neurobehavioral enhancement of residual brain function and may promote frontal activity by enhancing frontal–parietal connections. The parietal cortex may thus be an alternative for rTMS therapy protocols.

1. Introduction

Prolonged disorders of consciousness (pDoC) are a category of disorders of consciousness (DoC) in which the disease course lasts more than 28 days [1]. pDoC is a pathologic state that follows severe craniocerebral trauma, or results from a degenerative or congenital nervous system disorders. There are a large number of patients with pDoC in both developing and developed countries [2,3]. Not only do patients with pDoC may suffer considerably from many complications [4], their caregivers may also suffer from substantial ongoing psychosocial and economic burdens [5]. Thus, finding ways to promote the recovery of consciousness is conductive to both the patient's functioning and relieving the caregiver burden.

There are many current treatments for pDoC [6], including pharmacotherapy and non-pharmacotherapy approaches [7]. Neuromodulation, which is among the most important non-pharmacotherapy interventions, includes invasive and noninvasive protocols.

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Abbrevation

rTMS	repetitive transcranial magnetic stimulation
pDoC	prolonged disorders of consciousness
CRS-R	Coma Recovery Scale-Revised
ERP	Event-related potential
M1	Primary motor cortex
tDCS	Transcranial direct current stimulation
RMT	Resting motor threshold
EEG	Electroencephalography
TFA	Time-frequency analysis
STFT	Short-time Fourier transformation
MCS	Minimally conscious state
UWS	Unresponsive wakefulness syndrome

Invasive neuromodulation (i.e. deep brain or spinal cord stimulation) achieves direct contact with the target region. Its disadvantages include being invasive, expensive, and involving ethical issues that restrict its clinical use. Noninvasive neuromodulation avoids such disadvantages. Repetitive transcranial magnetic stimulation (rTMS), among the classical noninvasive modulation interventions, also has the advantages of being precise, cost effective, and safe. rTMS achieves it effects by depolarizing neurons within a transient generated time-varying magnetic field [8]. High-frequency and high-intensity rTMS can induce excitatory effects no matter in healthy subjects [9,10] or neuropsychiatric patients. And its neuromodulatory effects in pDoC have been confirmed repeatedly [11,12] since its use in this condition was first reported 1999. The rTMS target choice is among the most important protocol considerations. Previous target studies have focused on the dorsolateral prefrontal cortex [13–16] and the primary motor cortex (M1) [17,18]. In the choice of M1, the results showed no any clinical changes in the aspect of consciousness recovery. As for studies of DLPFC, some of them showed that MCS could gain most from it, others showed that both MCS and UWS could benefit from it. The inconsistency among these studies demonstrated that the targets applied in current studies were not universally applicable ones. For different pDOCs, especially who suffered from frontal cortex lesion, applying rTMS to a relatively complete region maybe a better choice, and benefit more from it. For pDoCs with different etiology and lesions, single target selection (DLPFC), might not meet the clinical needs. It is essential to seek alternative targets in making optimal rTMS protocol for them. Recent research has shown that the origin of consciousness is more relevant to the parietal regions [19]. Frontal-parietal network was crucial in consciousness, most investigators paid attention to frontal cortex, few noticed the parietal cortex. Recently, some researchers come to realize the importance of it, they applied parietal transcranial direct current stimulation (tDCS) to parietal cortex. When tDCS was recently applied to patients with pDoC, it demonstrated modulation effects in the recovery of consciousness [20–23]. Thus, we supposed that the parietal cortex is a potential target for rTMS protocols. And applying rTMS to parietal cortex could help the recovery of consciousness in pDoC.

In the evaluation of pDoC, Coma Recovery Scale-Revised (CRS-R) is the most common used scale to evaluate the changes in clinical behavior which is related to the consciousness. Electrophysiology is a widely used, objective method for assessing level of consciousness in patients with pDoC. This relatively inexpensive, practical technique includes many categories [24]. The P300 is an event-related potential (ERP) index that can be evoked by specific auditory stimulation paradigms. Those most commonly applied in pDoC are the oddball paradigms (i.e., a series of similar stimuli mixed with contrasting stimuli). The P300 is a primary positive ERP waveform, which presents around 300 ms after the stimulus. And its amplitude varies with the proportion of stimuli, the lower the proportion, the higher the amplitude. It reflects elaborate cognitive information processing [25]. Its use in detecting the signs of consciousness in pDoC has been confirmed [26] and it can thus be applied as an index for evaluating treatment response effects [24].

To verify whether the parietal cortex is an alternative effective target in the recovery of consciousness, this study applied parietal rTMS to patients with pDoC. CRS-R was applied to evaluate the effectiveness of it in promoting the recovery of consciousness. The appearance of P300 and the changes of P300 amplitude could reflect the cognitive information processing in brain. Topographic map and time-frequency analysis could better help us understand the induced brain activities. The goal of this study program in to provide the basis for a novel potential rTMS protocol target.

2. Materials and methods

2.1. Participants

Twenty-six patients with pDoC were recruited from the Department of Rehabilitation Medicine of Xuan Wu Hospital, Beijing, China. Inclusion criteria were: (1) DoC diagnosis based on repeated Coma Recovery Scale-Revised (CRS-R); (2) DoC duration is >1 month; (3) in stable condition; and (4) no improvement in state of consciousness >1 month. Exclusion criteria were: (1) history of neurological diseases or psychiatric disorders; (2) using drugs or undergoing any other treatment that may affect the cortical excitability; (3) epilepsy or frequent, uncontrolled spontaneous movements; (4) pacemakers; and (5) craniotomy or metallic implantation around the parietal regions.

Ethical approval for the study was provided by the ethics committee of Xuan Wu Hospital (2022-022; approved April 13, 2022). All

patients' families signed the written informed consent.

2.2. Experimental design

Twenty-six patients with pDoC were randomly assigned to two groups: rTMS (n = 13) or sham (n = 13). The method of randomization used in the study was simple randomization. The process was based on Excel (version 16.78.3) software. 26 random numbers were generated through the rand function of the software. Then, sort the 26 numbers according to the size of the number. The number of the first 13 belonged to the rTMS group while the number of the last 13 belonged to the sham group. It was a single-blind study and the patients did not know what group they were. General patient condition in each group is displayed in Table 1. Each study participant received stimulation once daily for 10 consecutive working days. The rTMS group received 10 sessions of rTMS stimulation; the sham group received 10 sessions of sham stimulation, as described in section 2.3. CRS-R and ERP were performed before and after the 10 stimulation days, as shown in Fig. 1.

2.3. rTMS stimulation protocol

Before starting the 10-day stimulation protocol, resting motor threshold (RMT) was determined (details shown in Fig. 2a). Disposable surface electrodes were placed on the right-hand abductor pollicis brevis to record the electromyography signals. The figure-of-eight focal TMS coil (Magstim Company Limited, Whitland, UK) was placed on the left M1 to induce muscle movement. Viking Quest Electrodiagnostic system (Natus Neurology Incorporated, Wisconsin, Amercia) was applied to record the contractions of abductor pollicis brevis. It contained hardware control components to mounting the electrodes and software control components to display the amplitude of the muscle responses. According to the recommendations of the International Federation of Clinical Neurophysiology Committee [27], the RMT was defined as the lowest intensity needed to evoke at least 5 out of 10 contractions with a peak-to-peak amplitude of $>50\ \mu$ V of the relaxed abductor pollicis brevis.

After RMT measurement, the rTMS group was administered 10 Hz rTMS at the parietal region (Fig. 2b). Repetitive mode TMS pulses were delivered by a figure-of-eight focal coil, which was placed over the parietal region-precuneus (Pz, according to the international 10–20 system for electroencephalography [EEG]). A total of 1000 pulses were delivered across 10 trains, at a frequency of 10 Hz (each train lasted 10 s, with 30 s inter-train intervals). Each participant's intensity was set to 90 % their RMT (which is in accordance with safety guidelines and previous of 10 Hz rTMS applied in pDoC) and the coil was placed tangentially.

For the sham group, the parameters were the same as the rTMS group protocol, except that the intensity was equal to 0 (i.e., the coil was angled 90 ° from the head or positioned away from the head).

Table 1
Clinical data of patients with pDoC.

Group	Patients	Diagnosis	Gender	Age (year)	Course (month)	Etiology	CRS-R
rTMS	P1	MCS	Female	53	6.5	hemorrhage	10
	P2	MCS	Male	32	4	Traumatic	8
	P3	UWS	Female	65	5	hemorrhage	4
	P4	MCS	Male	32	5	Traumatic	12
	P5	MCS	Male	35	7	hemorrhage	11
	P6	MCS	Female	53	12	hemorrhage	12
	P7	MCS	Female	56	5	Traumatic	8
	P8	MCS	Female	18	3	Traumatic	11
	P9	UWS	Male	68	1	ischemic	4
	P10	MCS	Female	70	10	hemorrhage	12
	P11	MCS	Male	59	8.5	hemorrhage	9
	P12	MCS	Male	32	4	Traumatic	8
	P13	MCS	Female	18	7	Traumatic	17
sham	P1	MCS	Female	53	6.5	hemorrhage	12
	P2	MCS	Male	32	4	Traumatic	8
	P3	MCS	Female	57	2	hemorrhage	10
	P4	MCS	Male	32	5	Traumatic	14
	P5	MCS	Male	35	7	hemorrhage	11
	P6	MCS	Male	71	7	Traumatic	9
	P7	MCS	Male	71	7	Traumatic	9
	P8	MCS	Male	65	1	hemorrhage	13
	P9	MCS	Male	32	4	Traumatic	14
	P10	MCS	Male	80	1	ischemic	20
	P11	MCS	Female	64	1	hemorrhage	10
	P12	MCS	Female	63	8	Tumor	9
	P13	MCS	Female	18	3	Traumatic	12

rTMS = repetitive transcranial magnetic stimulation; P = patient; MCS = minimally conscious state; UWS= Unresponsive wakefulness syndrome; CRS-R=Coma Recovery Scale-Revised. Six subscales score of CRS-R indicating the assessment of auditory, visual, motor, verbal, communication functions and arousal.

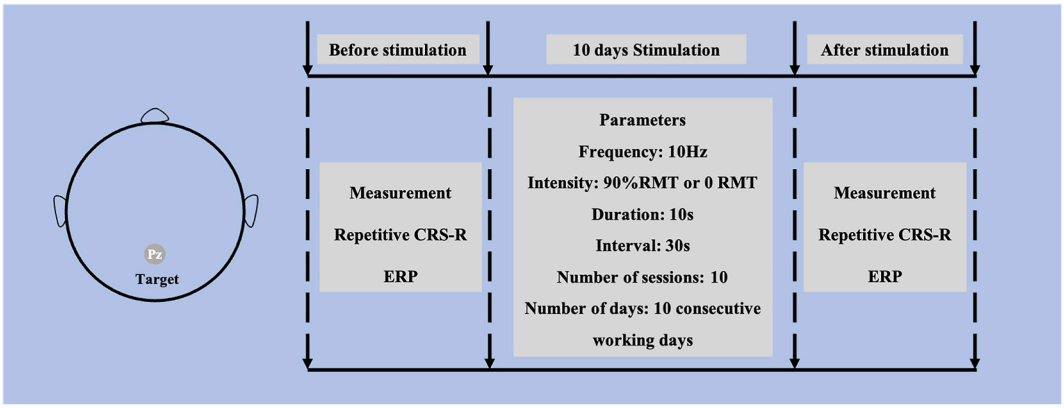

Fig. 1. Flow chart showing the experimental design.

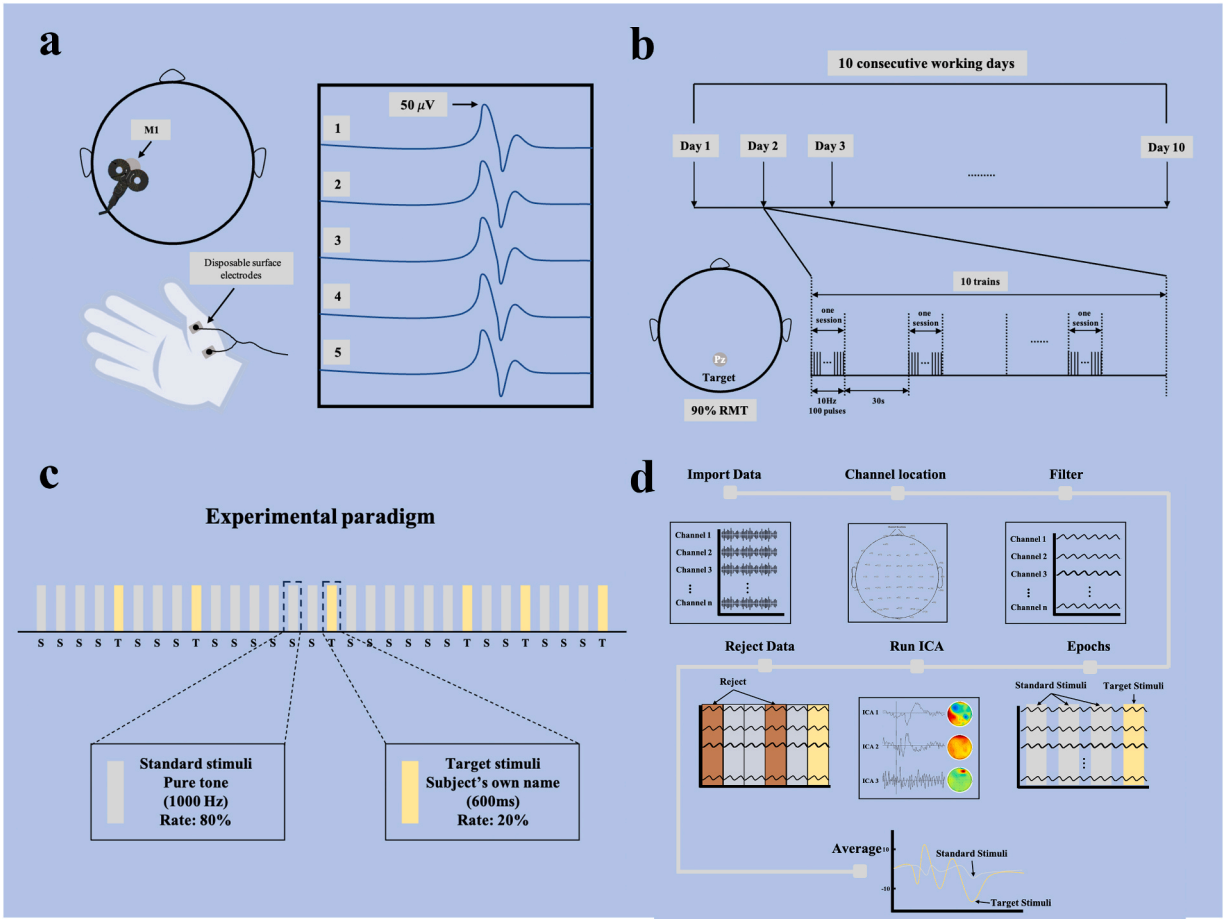

Fig. 2. The protocol of rTMS stimulation and data process. (a) The measure of resting motor threshold (RMT). (b) The protocol of parietal rTMS. All patients received 10 Hz rTMS or sham stimulation for 10 consecutive working days over the parietal cortex. (c) The paradigm of the auditory event-related potentials (ERP). It contained two types of stimuli: standard stimuli (pure tone), occupied 80 %; target stimuli (subject's own name), occupied 20 %. They appeared randomly. (d) The EEG preprocessing steps and the generation of P300.

2.4. Behavioral assessment

The CRS-R scale is a clinical evaluation tool to used characterize level of consciousness and monitor neurobehavioral recovery in patients with pDoC. Repeated CRS-R was used herein to reduce the misdiagnosis (the rate of which can be as high as 40 % [14] in single

evaluation of previous studies, five assessments within one week in the study). All participants were also administered the repeated CRS-R assessments after the 10-day stimulation protocol. The highest baseline CRS-R score was taken as the basis for the diagnosis. All CRS-R assessments were performed by a single, experienced physician who was blinded to the study condition.

2.5. ERP measurement

ERP data were recorded before and after the 10 stimulation sessions. The auditory oddball paradigm was used, the details of which have been described previously [28]. In the paradigm, the target stimulus (the participant's own name, 600 ms, intensity 90 dB) occupied 20 % and the standard stimulus (pure tone, frequency 1000 Hz, intensity 90 dB) occupied 80 %. S and T appeared randomly among the stimuli (Fig. 2c).

EEG signals were continuously recorded by an EEG Ag/AgCl cap of Neuroscan (Compumedics Limited, Victoria, Australia) with 64 channels. The EEG sampling rate was 1000 Hz and electrode impedance was kept <5 K Ω throughout. The participant was kept awake during the EEG recordings. The CRS-R arousal facilitation protocol was performed if the patient showed signs of sleepiness, and the experiment was suspended in the event of swallowing, sweating, or uncontrolled head movement.

2.6. EEG pre-process and process

Each step (Fig. 2d) was carried out using the EEGLAB platform, a plug-in unit of Matlab R2013b (Mathworks, Natick, MA, USA). EEG data were imported into the EEGLAB, edited for channel location and referenced to the nose tip. Filters were set to 0.1–30 Hz. The EEG data were segmented into 2-s epochs. All data were scanned to interpolate poor signals, and epochs with artifact were rejected. Independent component analysis was also run to reject artefacts from eye blinks and ocular and head movements. Data $>100\,\mu V$ were also rejected. The P300 waveform, induced by different stimuli, was identified by data averaging. Every patient could form a two-dimension P300 data (containing the information about channel*time). Aggregate every patient's P300 data information to form a three-dimension database which containing subjects*channel*time. Select the Fz, Cz and Pz channels, respectively. Average the database in 'subjects' dimension, and the P300 data at group level was obtained. Use the 'find' function of Matlab to search the time point of P300 amplitude. And plot the topographic map at this point. The process of P300 waveform and topographic map was all achieved by the coding based on Matlab R2013b (Mathworks, Natick, MA, USA).

The time-frequency analysis (TFA) process was based on the functions in Matlab R2013b (Mathworks, Natick, MA, USA). The main steps were as follows: (1) Set the window size as 200 ms; (2) Intercept the signals according to the windows size across the data periods; (3) The intercepted the signals then undergo the short-time Fourier transformation (STFT); and (4) Average the post-STFT across the epochs for each electrode and calculate the average power for each frequency (1–30 Hz).

2.7. Statistical analysis

Statistics were performed via SPSS version 26.0 (SPSS, Chicago, IL, USA). Independent-samples *t*-test were used to compare the demographic and clinical characteristics (age, disease course and etiology) between the groups. Measurement data were expressed by X ± SD. Repeated measures analysis of variance were applied to verify the changes between groups (rTMS group and sham group) and times (the time of CRS-R measure: before and after stimulation). Then pDoC patients were divided into two subgroups (traumatic brain injury and non-traumatic brain group) to determine that whether there was a difference in repose to rTMS between patients with traumatic brain injury (TBI) and non-TBI.

P300 measurement was carried out in EEGLAB platform, Matlab plugin R2013b (Mathworks, Natick, MA, USA). P300 amplitude before and after the 10-day stimulation protocol was made with repeated measures analysis. Time and frequency domain differences before and after the 10-day stimulation protocol were also compared using paired-samples *t*-tests, with false discovery rate correction. $P < 0.05$ was considered statistically significant.

Correlation analysis was applied to analyze the relationship between P300 amplitude and CRS-R scores. Pearson's correlation coefficient for normal data and Spearman's correlation coefficient for non-normal data.

3. Results

3.1. Group demographic and clinical characteristics

Demographic and clinical characteristics for the 26 enrolled patients with pDoC are shown by group in Table 1. There were no significant between-group differences in age, disease course, or etiology. Before stimulation, the CRS-R score was 9.69 ± 3.50 in rTMS group while the score was 11.62± 3.20 in sham group. After stimulation, the scores changed to 11.54± 33.64 and 12.08± 3.25, respectively. And the results of repeated measures analysis showed that the CRS-R scores before and after stimulation were different ($F = 13.203$, $p = 0.001$) in measurement time. Besides there was an interaction in times and groups ($F = 4.753$, $p = 0.039$). By comparison, the CRS-R scores increased significantly after rTMS ($P = 0.00039$) while the scores of sham did not show this change ($P = 0.314$). In the subgroup analysis, we analyzed the effects in TBI group and non-TBI group. In TBI group, the results showed that the within-subjects effects of time was significant ($F = 6.038$, $P = 0.034$) and there was an interaction in time and groups ($F = 6.038$, $p = 0.034$). The CRS-R of TBI-rTMS group increased from 10.67 ± 3.56 to 13.33± 3.56. While the score of TBI-sham group remained 11.00 ± 2.68 after stimulation. As for non-TBI, there was no significant change in within-subjects effects ($F = 0.194$, $P = 0.668$) and between-

subjects effects (F = 2.913, P = 0.114).

3.2. ERP

Figs. 3 and 4 showed the grand averages for the P300 waveform in the rTMS and sham groups, respectively, at Fz, Cz, and Pz. Before the 10-day stimulation protocol, no P300 waveforms were detected in either group (Fig. 3a, d, 3h and Fig. 4a, d 4 h). After the 10-day protocol, the rTMS group showed a P300 waveform in Fz (Fig. 3b), Cz (Fig. 3e), and Pz (Fig. 3i),. For P300 in Fz, the results of repeated measures analysis showed that the within effects of measurement time did not make a difference (F = 0.155, P = 0.698). However, there was an interaction in time and groups (F = 6.905, P = 0.016). By comparison, the value significantly increased after receiving rTMS (P = 0.045) while these changes did not show in sham group (P = 0.13). As for Cz and Pz, the results of repeated measures analysis showed no statistical significance no matter in measurement time (F = 1.792, P = 0.196; F = 1.405, P = 0.25) or interaction in time and groups (F = 2.894, P = 0.104; F = 0.185, P = 0.672). In rTMS group, there was also an increase in potentials on topographic mapping of P300 (Fig. 5c and d), especially in the left prefrontal cortex (Fig. 5d). After 10 days of sham sessions, the sham group continued to show no P300 waveforms (Fig. 4b, e and 4i). And the topographic mapping showed no obvious changes in voltage (Fig. 5a and b).

3.3. Time-frequency analysis of P300 in rTMS stimulation

After the 10-day rTMS stimulation protocol, the rTMS group showed an increased in the theta and delta band power of P300 at Fz (Fig. 6a and b), Cz (Fig. 6d and e), and Pz (Fig. 6g and h) electrodes, though this change was not statistically significant (P > 0.05, Fig. 6c, f and 6i).

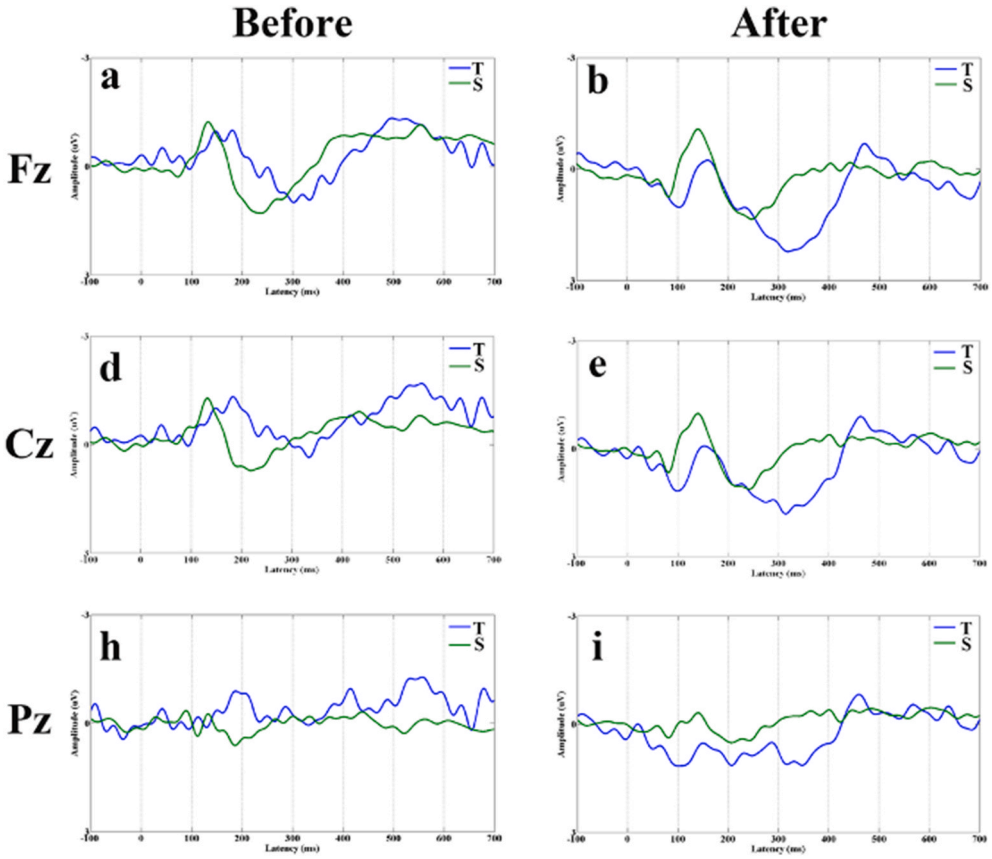

Fig. 3. P300 of rTMS group. (a), (b), (d), (e), (h), (i) Blue solid lines presented the event-related potential induced by target stimuli, green solid lines presented the event-related potential induced by standard stimuli. In the auditory paradigm, P300 is a positive waveform appears around 300 ms elicited by the target stimulus. In Fz, Cz and Pz, there were no P300 before stimulation, while the P300 occurred after stimulation. S, standard stimuli; T, target stimuli. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

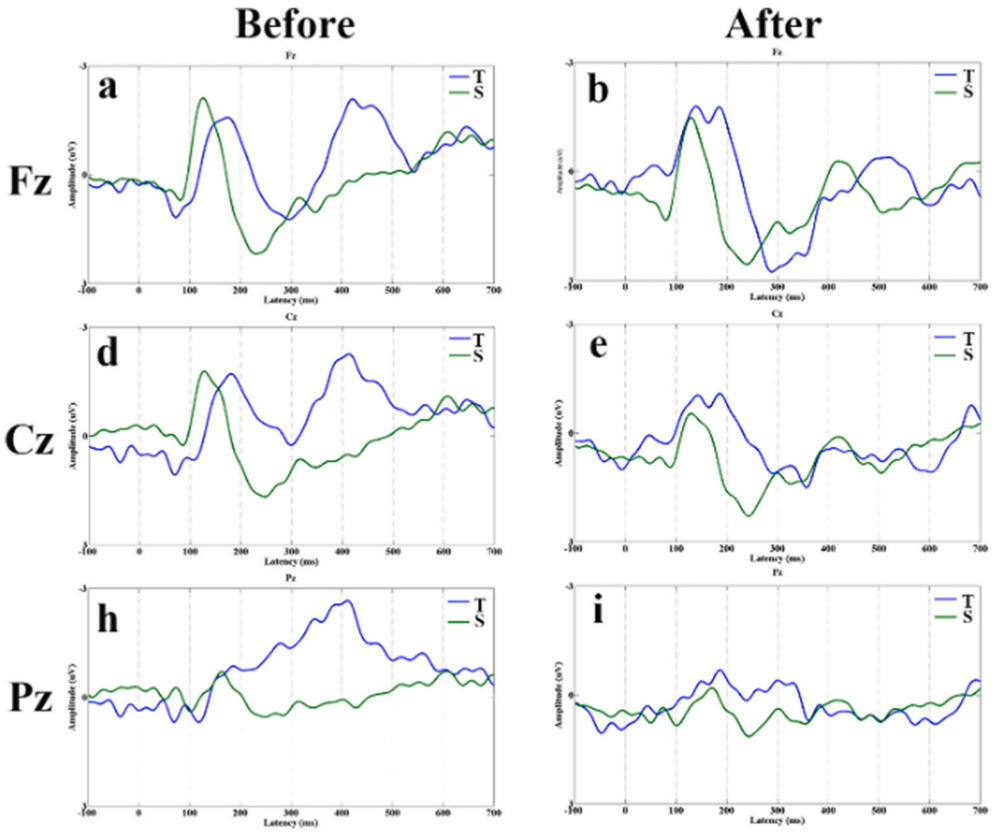

Fig. 4. P300 of sham group. (a), (b), (d), (e), (h), (i) Blue solid lines presented the event-related potential induced by target stimuli, green solid lines presented the event-related potential induced by standard stimuli. In the auditory paradigm, P300 is a positive waveform appears around 300 ms elicited by the target stimulus. In Fz, Cz and Pz, there were no P300 before and after stimulation. S, standard stimuli; T, target stimuli. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

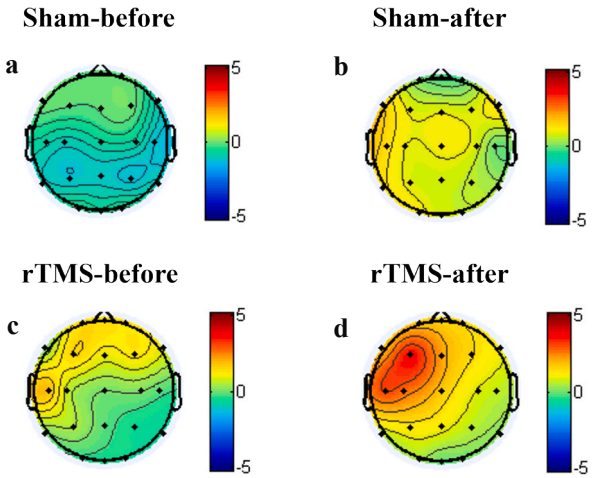

Fig. 5. (a) Topographic map of real rTMS group around 300 ms before the stimulation. (b) Topographic map of real rTMS group around 300 ms after the stimulation. (c) Topographic map of sham group around 300 ms before the stimulation. (d) Topographic map of sham group around 300 ms after the stimulation. The higher the value, the brighter the color. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

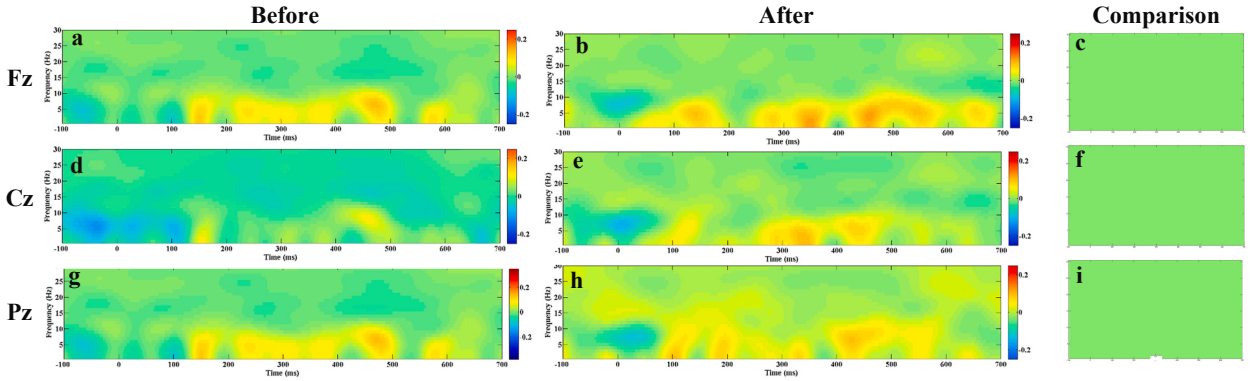

Fig. 6. Time-Frequency analysis of rTMS group (a) The result before the stimulation in Fz. (b) The result after the stimulation in Fz. (d) The result before the stimulation in Cz. (e) The result after the stimulation in Cz. (g) The result before the stimulation in Pz. (h) The result after the stimulation in Pz. Different colors represent different values of power. The brighter the color, the higher the value. The changes in color could reflect the changes in the power of different frequency band. (c) The comparison in Fz. (f) The comparison in Cz. (i) The comparison in Pz. The appearance of red area in the comparison box indicated statistical significance (compare the power values before and after rTMS). The significance was set as 0.05. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.4. Correlations between P300 amplitude and CRS-R values in rTMS group

Before rTMS stimulation, the P300 amplitude showed no correlation with CRS-R values ($r = 0.486$, $P = 0.130$). And there also showed no correlations between P300 amplitude and CRS-R values after rTMS stimulation ($r = 0.045$, $P = 0.895$).

4. Discussion

To date, finding effective ways to promote levels of consciousness in patients with pDoC remains a challenge. rTMS is a promising intervention due to its being noninvasive, precise, relatively inexpensive, and having few ethical issues. Its use in pDoC has also been increasing in recent years. Just similar to another classic noninvasive intervention, tDCS, rTMS has usually been used to target the dorsolateral prefrontal and M1 cortices. However, investigators have speculated that the parietal cortex is a critical consciousness-associative cortical region. Thus, we targeted the parietal cortex to determine whether it is an effective alternative rTMS protocol target. Although high frequency (>1 Hz) rTMS can increase cortical excitability, it may also induce seizures. Higher frequencies increase this risk. And 10 Hz was the most commonly used parameter in the protocol of rTMS with few adverse events reported [11]. For safety, we chose 10 Hz and 90 % RMT.

Herein, CRS-R score results demonstrated that parietal rTMS may promote consciousness in patients with pDoC. After 10 days of stimulation sessions, CRS-R scores changed significantly in the repeated measures analysis, times and groups had an interaction. The changes of rTMS group were larger than those of sham group. Thus, rTMS had the effects in increasing the CRS-R scores. The CRS-R score is both a well-recognized behavioral scale used to diagnose pDoC, and an index used to assess response to consciousness-promoting interventions. The significant increase in CRS-R scores in the rTMS group indicates that the parietal cortex is a promising rTMS target in pDoC.

However, factors including operator experience and patient motor dysfunction and pain render the CRS-R a subjectivity scale. Thus, electrophysiology was also applied herein, to evaluate the neurobehavioral effects of parietal rTMS and its underlying mechanism. ERP is an objective, convenient assessment for evaluating the level of consciousness in pDoC [14]. Studies have used the P300 waveform, an ERP index correlated with attention and conscious perception, to assess the residual cortical information processing capabilities in pDoC [6]. It can be used as an index for predicting the consciousness recovery [29] and evaluating the effects of noninvasive neuromodulations [30]. The P300 amplitude can vary according to the amount of focal attention on a discriminate stimulus. Thus, increased P300 amplitude reflects greater attention resource allocation. It may also be related to the improved residual brain function and consciousness. Herein, no P300 waveforms were detected in either group before the 10-day stimulation protocol. After the protocol, the P300 waveform appeared in the rTMS group, but not the sham group, indicating that among patients with pDoC, rTMS may restore attention resource allocation abilities and enhance residual brain functions.

EEG activity is a marker of cortical activation. Previous studies have observed neuronal oscillations in different EEG frequency bands when applying rTMS to different brain cortices. rTMS to the motor cortex may induce alpha and beta power shifts, while rTMS in the dorsal premotor cortex (a part of the frontal cortex) may cause theta and delta frequency band reactivity [17,31,32]. Alpha band oscillations are modulated by GABA levels, while theta and delta band activities are more related to dopamine. Herein, TFA was used to analyze the oscillations in P300 induced by parietal rTMS. In the TFA at Fz, Cz, and Pz, an increase was detected in the theta and delta bands. These results in this study are similar to those induced by rTMS to the dorsal premotor cortex. In the current study, changes occurred not only occur in the parietal region; those most noticeable were at the frontal electrodes (Fz). This might be explained by the functional anatomy of the target, the precuneus. The precuneus is part of the posterior parietal cortex. Its deactivation has been related

to the physiology of altered states of consciousness (e.g., slow-wave sleep, rapid eye movement sleep, the hypnotic state, vegetative state) and some neuropsychiatric conditions with reduced self-awareness (e.g., Alzheimer's disease, schizophrenia, epilepsy) [33]. It has the cortical connections with the dorsolateral prefrontal cortex, but is void of any connections with the M1. A recent study [34] of conscious awareness also demonstrated that the prefrontal activity is triggered by neural signal transfer originating from the posterior brain region, specifically the precuneus. And the neural signal referred to the theta oscillations in EEG. Herein, the topographic maps showed that parietal rTMS elicited pronounced P300 effects, especially in the left frontal cortex. By combining TFA with topographic maps, we conjecture that stimulating the parietal cortex could promote frontal activity by enhancing the frontal–parietal connections, ultimately promoting recovery of consciousness.

In order to determine the relationship between the recovery of consciousness and the results of ERP, we correlated P300 amplitude with the CRS-R scores before and after rTMS stimulation. Pearson's correlation coefficient and Spearman's correlation coefficient were both linear indicators, and the results showed no correlation according to the linear indicators. On the one hand, these results might indicate that there was no linear relationship between P300 amplitude and CRS-R scores. However, it cannot be ruled out that there may be a non-linear relationship between the two. On the other hand, it might indicate that there was indeed no correlation between the two in the study. It could be due to the small samples, the correlation between the two is difficult to display. The relationship could only be demonstrated after recruiting more patients in the follow-up study. Besides, other factors may also contribute the outcome. The ERP evaluation is an objective and sensitive test that reflects the transient changes while the CRS-R scores reflect the clinical behavioral change which is a slow process. The neuromodulation effects of rTMS were fully displayed in the ERP but not yet fully manifested in the CRS-R scores. Thus, the last CRS-R score may not adequately, just partly reflects the state of consciousness after receiving rTMS. As a consequence of this, it might affect the results of the correlation.

Though these results confirmed the effectiveness of parietal rTMS in pDoC, the study was not without limitations. First, the TFA results just demonstrated an increase, not a statistically significant change. We suspect that this was due to the relatively small sample size, which limited the detection of TFA-based changes from parietal rTMS. Subsequent studies should include more patients with pDoC to validate these effects. Second, degree of pDoC may play a role in different responses to parietal rTMS. Limited by small sample size, the patients enrolled in our study was more about MCS. Besides, patients in rTMS group had longer disease course and lower baseline CRS-R compared to the sham group. Though there showed no difference between in age, course statistically and the parietal rTMS still showed its effects, a larger sample size was needed to balance these factors in the future study. Third, we only analyzed the EEG index for P300. Neuroimaging technology is a valuable tool for evaluating connections among cortices, and could facilitate our deeper understanding of these mechanisms. Finally, this study only investigated the neuromodulation effects of 10 sessions of parietal rTMS. The prognosis for 12-month recovery of consciousness is also essential among patients with pDoC. These issues should all be considered in subsequent trials.

5. Conclusion

Parietal rTMS promoted recovery of consciousness in patients with pDoC. The increase in P300 amplitude further supports its positive efficacy. In addition, topographic maps and changed P300 power in the delta and theta band frequencies suggest that parietal rTMS may achieving the effects by promoting frontal cortex activity. Our results demonstrate that parietal rTMS is a promising intervention for recovery of consciousness in patients with pDoC. The parietal cortex may thus be a feasible alternative target in rTMS protocols.

Institutional review board statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Xuan Wu Hospital (approval number:2022-022; approved April 13, 2022).

Informed consent statement

Informed consent was obtained from all patients' families involved in the study. In the informed consent, all patients agreed to participate the study. Besides, they agreed to publish the data of participants is required.

Data availability statement

The data used and/or analyzed for the study are available from the corresponding author on reasonable request.

Declaration of generative AI in scientific writing

No use of generative AI and AI-assisted technologies in the writing process.

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CRediT authorship contribution statement

Xiaoping Wan: Writing – original draft, Validation, Software, Methodology, Formal analysis. **Ye Zhang:** Project administration. **Yanhua Li:** Investigation. **Weiqun Song:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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