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Original Article

Mechanisms of arousal promotion and cortical plasticity induced by multi-target transcranial magnetic stimulation in patients with chronic disorders of consciousness

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Abstract: Objective: To evaluate the arousal-promoting effect of multi-target transcranial magnetic stimulation (MT-TMS) in patients with chronic disorders of consciousness (DOC) and the mechanisms underlying cortical plasticity. Methods: Eighty-six patients with chronic DOC treated at our institution from January 2024 to December 2025 were retrospectively identified. According to the stimulation approach, they were assigned to a multi-target stimulation group (MTG, n=43, combined stimulation of the left dorsolateral prefrontal cortex [L-DLPFC] and the right primary motor cortex [R-M1]) and a single-target stimulation group (STG, n=43, stimulation of only the L-DLPFC). The two groups were compared for levels of consciousness before and after treatment, electroencephalographic (EEG) activity, cortical excitability, brain functional connectivity, neuroelectrophysiological indicators, and incidence of adverse reactions. Results: After 4 weeks of treatment, the MTG showed markedly higher CRS-R total score than the STG ($P<0.05$). The MTG exhibited markedly increased EEG α power and α/δ ratio than the STG ($P<0.05$). The MTG had markedly greater MEP amplitude and longer CSP duration than the STG ($P<0.05$). The frontal-parietal functional connectivity strength was stronger in the MTG ($P<0.05$). The MTG had markedly higher consciousness recovery rate than the STG (37.21% vs. 16.28%) ($P<0.05$). The incidence of adverse reactions did not differ markedly between the two groups ($P>0.05$). Conclusions: MT-TMS improves consciousness levels, regulates EEG activity, enhances cortical excitability and inhibitory regulation, and facilitates frontal-parietal functional connectivity in patients with chronic DOC.

Keywords: Transcranial magnetic stimulation, chronic disorders of consciousness, multi-target stimulation, cortical plasticity, arousal therapy, brain functional connectivity

Introduction

Chronic disorders of consciousness (DOC) are characterized by a persistent impairment of consciousness caused by various etiologies and primarily include vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) [1]. Epidemiological data indicate that approximately 100,000 new cases of DOC occur annually in China, and the total number of affected patients exceeds 500,000, posing a significant burden on patients' families and society [2]. The likelihood of recovery of consciousness in patients with DOC is strongly associated with disease duration, etiology, and age; however, the overall prognosis remains dismal [3].

Currently, treatment approaches for DOC mainly include pharmacological therapy, hyperbaric oxygen therapy, sensory stimulation, deep brain stimulation, and noninvasive brain stimulation. As a safe and noninvasive technique, transcranial magnetic stimulation (TMS) induces currents in the cerebral cortex by generating a time-varying magnetic field on the scalp, thereby modulating neuronal excitability and plasticity. Recently, TMS has been widely used in patients with DOC. Multiple studies have validated its arousal-promoting effects in some patients [4, 5]. In conventional TMS protocols, a single-target stimulation approach typically is used, with commonly targeted regions including the left dorsolateral prefrontal cortex (L-DLPFC), primary motor cortex (M1), and posterior pari-

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etal cortex. However, impaired consciousness in patients with DOC is associated with dysfunction in multiple brain regions and neural circuits, including the default mode network, executive control network, and salience network. Single-target stimulation may be insufficient to fully activate these impaired networks [6].

From a theoretical perspective, multi-target stimulation may simultaneously act on multiple key brain regions, thereby enhancing functional connectivity between neural networks through synergistic effects and promoting cortical plasticity, which may contribute to improvements in arousal. Existing research has started to explore the clinical effects of simultaneous or sequential multi-site neuromodulation. Huang et al. [6] systematically reviewed the application of TMS in DOC and emphasized the theoretical advantages of targeting multiple nodes of the frontoparietal consciousness network. Avalos-Alais et al. [7] demonstrated through high-resolution electrophysiological investigation that effective connectivity within the lateral prefrontal cortex extends extensively to parietal regions, providing neuroanatomical evidence for the combined stimulation of the prefrontal and motor/parietal targets. These findings collectively suggest that stimulating multiple network nodes may be more effective in restoring damaged large-scale neural communications in DOCs compared with single-target approaches.

To date, few studies have compared multi-target versus single-target TMS for arousal therapy in patients with DOC. The therapeutic advantages of multi-target stimulation and its underlying neural mechanisms remain to be fully elucidated. This retrospective controlled study compared the arousal-promoting effects of multi-target and single-target TMS in patients with chronic DOC and investigated the underlying mechanisms of cortical plasticity, aiming to provide evidence for optimizing clinical arousal therapy in DOC.

Methods

Research design

This retrospective controlled study was granted permission by the Ethics Committee of Shanghai Tenth People's Hospital, Tongji University School of Medicine and performed in accordance with the Declaration of Helsinki. Patients with chronic DOC who were hospitalized in the Department of Rehabilitation Medicine of our institution from January 2024 to December 2025 were identified from the hospital medical system.

Inclusion criteria: (1) Patients were diagnosed with DOC [8] and confirmed as VS/UWS or MCS via Coma Recovery Scale-Revised (CRS-R) scale assessment; (2) Disease duration ≥ 28 days; (3) Age 18-75 years; (4) Stable vital signs without the need for mechanical ventilation; (5) Etiologies of traumatic and non-traumatic brain injuries (e.g., hypoxic-ischemic encephalopathy, stroke); (6) Relatively intact brain structure on cranial magnetic resonance imaging or computerized tomography.

Exclusion criteria: (1) Presence of intracranial metallic foreign bodies or implants; (2) History of epilepsy or electroencephalography (EEG) showing significant epileptiform discharges; (3) Presence of pacemaker implants; (4) Severe heart, lung, liver, or kidney dysfunction; (5) Large cranial defects; (6) Pregnant or lactating women; (7) Use of medications that may affect cortical excitability within 2 weeks before treatment; (8) Previous treatment with TMS.

Based on the aforementioned criteria, 86 patients were finally included. Of these patients, 43 patients received multi-target TMS and were assigned to the multi-target stimulation group (MTG), and 43 patients received single-target TMS and were assigned to the single-target stimulation group (STG).

The grouping of MTG or STG was determined by the attending physician based on patients' clinical conditions, comprehensive assessment of the rehabilitation team, and the availability of treatment resources at enrollment. No randomization was performed in group allocation. A post-hoc power analysis was performed for the included patients. Based on the primary outcome measure (difference in CRS-R total score: 2.72 points; pooled standard deviation: 3.10), the effect size was Cohen's d=0.88. With a two-sided $\alpha=0.05$ and statistical power =0.80, at least 42 patients were required in each group. The final sample size of 43 patients in each group met this requirement.

Treatment approaches

Patients in both groups underwent standard rehabilitation therapy, including proper limb placement, passive joint movement, sensory stimulation therapy, and nutritional support. Multi-target TMS (dual-target) therapy was performed in MTG. In this study, multi-target stimulation was specifically implemented as dual-target TMS, which combined stimulation of the L-DLPFC and the right primary motor cortex (R-M1).

Multi-target TMS was performed in the MTG. (1) Target localization for stimulation: Target localization was performed using the international 10-20 system. L-DLPFC was taken as the first target (F3 position) and R-M1 as the second target (C4 position). (2) Stimulation parameters: A figure-of-eight coil was used. High frequency TMS (10 Hz) at an intensity of 80% of the resting motor threshold (RMT) was applied to the L-DLPFC. Each train consisted of 20 pulses, with a total of 50 trains and a 10-second interval between trains. Low frequency TMS (1 Hz) at an intensity of 100% of the RMT was applied to the R-M1. Each train consisted of 5 pulses, with a total of 200 trains and a 1-second interval between trains. (3) Frequency of treatment: TMS was administered once daily. L-DLPFC was stimulated first, followed by stimulation of R-M1 with a 30-minute interval between stimulations, five days per week for four consecutive weeks.

Patients in the STG received only single-target TMS of the L-DLPFC. The stimulation parameters were identical to those used for L-DLPFC stimulation in the MTG. Treatment sessions were conducted once a day, five days per week, for a total of four consecutive weeks.

Outcome measures

Primary outcomes: (1) Assessment of consciousness level: The consciousness level was evaluated before treatment and 4 weeks after treatment using the CRS-R scale [9], consisting of six subscales, namely auditory (0-4), visual (0-5), motor (0-6), oromotor (0-3), communication (0-2), and arousal (0-3) functions, with total scores of 0-23. Higher total scores reflect better consciousness levels. (2) EEG activity indicators: The 32-channel EEG system was utilized to record EEG at rest. The absolute powers of δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), and β (13-30 Hz) waves, and the α/δ power ratio were analyzed. (3) Cortical excitability indicators: Motor evoked potential (MEP) amplitude and cortical silent period (CSP) duration, which reflect cortical excitatory and inhibitory functions, were assessed using the TMS [10].

Secondary outcomes: (1) Baseline data included age, sex, etiology, disease duration, classification of consciousness, and Glasgow Coma Scale (GCS) scores. (2) EEG functional connectivity analysis was used to calculate the phase lag index (PLI) between the frontal and parietal regions, which reflects their functional connectivity strength. (3) Neuroelectrophysiological indicators included the amplitude and latency of brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SEP). (4) The incidence of adverse reactions, including headache, dizziness, epileptic seizures, skin discomfort, and nausea, were recorded.

Statistical methods

Data were processed using the Statistical Package for Social Sciences (SPSS) Statistics 26. All continuous data were normally distributed as tested by the Shapiro-Wilk test and were described by mean ± standard deviation (SD). Comparisons between groups were analyzed using the independent samples t-tests. Categorical data were described by number of cases and percentages [n (%)] and analyzed using the χ^2 test or Fisher's exact test. Repeated measures analysis of variance (ANOVA) was used to compare changes in CRS-R total score and EEG band power at baseline and 4 weeks after treatment, with group as a between-subject factor and time as a within-subject factor. Statistical significance was set at $P<0.05$.

Results

Comparison of baseline characteristics

Both groups of patients did not differ markedly in terms of baseline characteristics, including sex, age, etiology, disease duration, classification of consciousness, and baseline GCS score ($P>0.05$), suggesting comparability between groups (**Table 1**).

Comparison of CRS-R scores

Before treatment, the CRS-R total score and subscale scores did not differ markedly between the two groups ($P>0.05$). After 4 weeks of treatment, the CRS-R total score of the MTG was markedly elevated compared with the STG [(12.58±3.24) vs. (9.86±2.95),

Table 1. Comparison of general data (mean ± SD)/[n (%)]

General data	Multi-target stimulation group (n=43)	Single-target stimulation group (n=43)	t/χ^2	P
Average age (years)	48.56±12.34	49.23±11.87	0.258	0.797
Men/Women	26/17	24/19	0.188	0.665
Disease duration (days)	68.42±23.56	71.35±25.12	0.560	0.577
Traumatic/non-traumatic etiology	19/24	21/22	0.186	0.666
VS/MCS	22/21	20/23	0.186	0.666
Baseline GCS score (points)	7.12±1.45	7.28±1.52	0.502	0.617
Hypertension	14 (32.56)	16 (37.21)	0.208	0.648
Diabetes	8 (18.60)	10 (23.26)	0.286	0.593
Total score of pre-treatment CRS-R	7.84±2.56	7.65±2.42	0.356	0.723
Pre-treatment α/δ power ratio	0.21±0.08	0.20±0.07	0.616	0.540

Note: CRS-R: Coma Recovery Scale-Revised; GCS: Glasgow Coma Scale; VS/MCS: vegetative state/minimally conscious state.

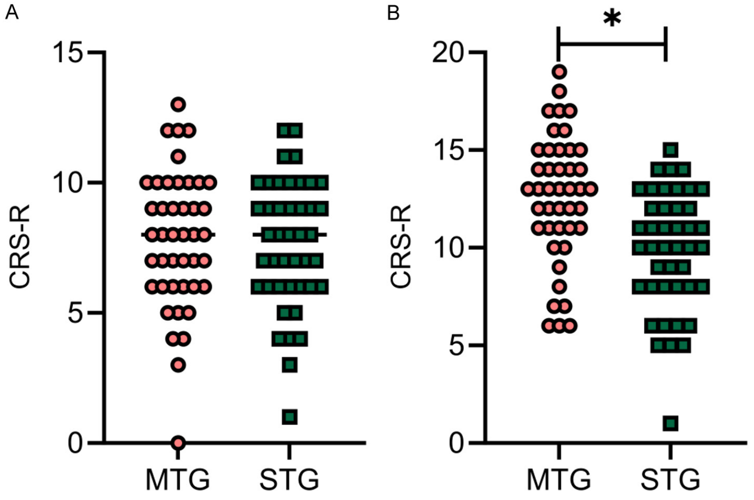

Figure 1. Comparison of CRS-R scores between the two groups. A. Before treatment, the CRS-R subscale scores did not differ markedly between the two groups (P>0.05). B. After 4 weeks, the MTG exhibited markedly elevated CRS-R scores than the STG (P<0.05). Note: CRS-R: Coma Recovery Scale-Revised; MTG: multi-target stimulation group; STG: single-target stimulation group. **P<0.01. n=43.

t=4.101, P<0.001]. After 4 weeks of treatment, the scores of auditory, visual, motor, and arousal functions were markedly higher in the MTG (P<0.05) (**Figure 1**).

Comparison of EEG activity indicators

The EEG activity indicators did not differ markedly between the two groups before treatment (P>0.05). After 4 weeks, the MTG exhibited higher α and β power (P<0.05), higher α/δ ratio [(0.36±0.10) vs. (0.26±0.09), t=4.918, P<0.001], and lower δ power than the STG (P<0.05). There was no statistically significant difference in θ power before and after treatment (P>0.05) (**Figure 2**). In a representative case, pre-treatment EEG revealed multiple irregular low-amplitude θ and δ waves in both hemispheres, with low-amplitude β (11.5-14 Hz) waves present in the frontal region, indicating the predominance of slow-wave activity. After 4 weeks of treatment, EEG showed numerous low-amplitude fast-wave activities in both hemispheres, mixed with low-amplitude 6-8 Hz waves. These findings indicate a shift of EEG activity toward normal arousal, with increased fast-wave activity and decreased slow-wave activity, consistent with the statistical analyses (**Figure 3**).

Comparison of cortical excitability indicators

MEP amplitude and CSP duration did not differ significantly between the two groups before treatment (P>0.05). After 4 weeks, the MTG demonstrated significantly greater MEP amplitude and longer CSP duration than the STG (P<0.05) (**Figure 4**).

Comparison of brain functional connectivity indicators

PLI values across frequency bands did not differ markedly between the two groups before treatment (P>0.05). After 4 weeks, the MTG exhibited markedly higher frontal-parietal PLI values in α and β frequency bands compared with the STG (P<0.05) (**Figure 5**).

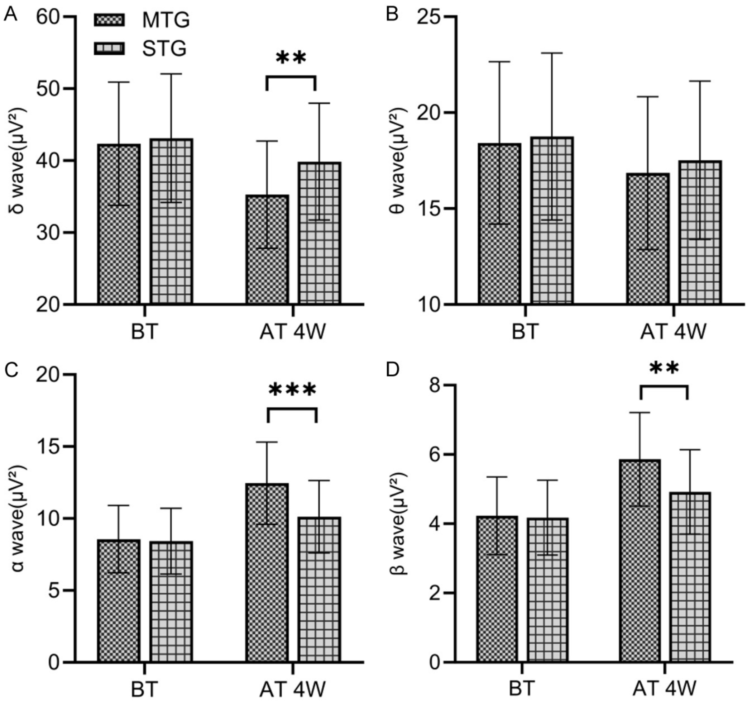

Figure 2. Comparison of EEG activity indicators between the two groups. Both groups showed no statistical significance in EEG activity indicators before treatment ($P>0.05$). After 4 weeks, the MTG exhibited significantly higher α (C) and β (D) power and lower δ power (A) than the STG ($P<0.05$). There was no statistically significant difference in θ power (B) before and after treatment ($P>0.05$). Note: EEG: electroencephalography; MTG: multi-target stimulation group; STG: single-target stimulation group. $^{**}P<0.01$; $^{***}P<0.001$. n=43.

Comparison of neuroelectrophysiological indicators

No marked differences in BAEP and SEP were observed between the two groups before treatment ($P>0.05$). After 4 weeks, the MTG demonstrated significantly shorter SEP-N20 latency and greater SEP-N20 amplitude than the STG ($P<0.05$) (**Figure 6**).

Comparison of incidence of adverse reactions

The overall incidence of adverse reactions was 18.60% (8/43) in the MTG and 13.95% (6/43) in the STG, exhibiting no marked difference between groups ($P>0.05$) (**Table 2**).

Discussion

Effect of multi-target TMS on consciousness levels

This study revealed that after 4 weeks, the MTG demonstrated significantly higher CRS-R total score and subscale scores than the STG. These findings suggest that multi-target TMS significantly improved levels of consciousness in patients with DOC. The L-DLPFC is a core node of the executive control network and is involved in higher cognitive functions. In addition, M1 is a critical region for motor functions and is closely associated with sensory integration and arousal. Multi-target stimulation activates both the executive control network and the sensorimotor network, enhancing brain regions associated with awareness through the synergistic effects between these networks [11, 12]. Consciousness disorders in patients with DOC are closely associated with impaired functional connectivity of the frontal-parietal network [13]. The multi-target stimulation strategy used in this study targets these two key regions and may facilitate consciousness recovery. In addition, high-frequency stimulation was applied to the L-DLPFC to enhance cortical excitability, whereas low-frequency stimulation was applied to the R-M1 to regulate intercortical balance. This differential stimulation protocol may help optimize the function of neural networks [14].

Effect of multi-target TMS on EEG activity

EEG activity reflects the brain functional state. In this study, the MTG had markedly higher α power and α/δ ratio and lower δ power than the STG after 4 weeks. Patients with DOC exhibit typical EEG features, including increased slow-wave (δ wave) activity, reduced fast-wave (α wave, β wave) activity, and a decreased α/δ ratio [15]. Alpha waves have close correlation with arousal and attention maintenance. Its increased power suggests improvements in cortical excitability and functional state. The EEG findings demonstrate that multi-target TMS more effectively regulates EEG patterns in DOC patients and facilitates their shift toward a normal arousal state. This finding verifies the assessment results of consciousness levels,

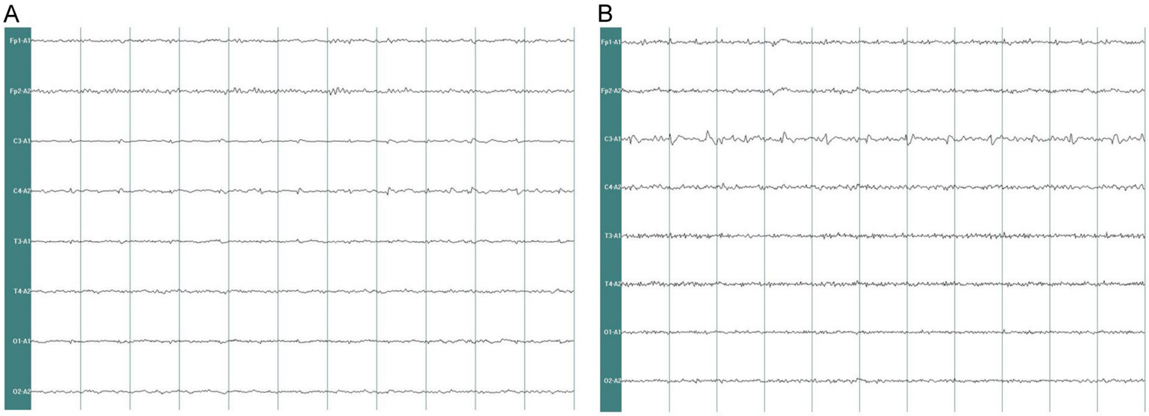

Figure 3. EEG of representative cases before and after treatment. A. Before treatment, the EEG revealed multiple irregular low-amplitude θ and δ waves in both hemispheres, with low-amplitude β (11.5-14 Hz) waves present in the frontal region. B. After 4 weeks of treatment, the EEG showed numerous low-amplitude fast waves in both hemispheres, mixed with low-amplitude 6-8 Hz waves. Note: EEG: electroencephalography.

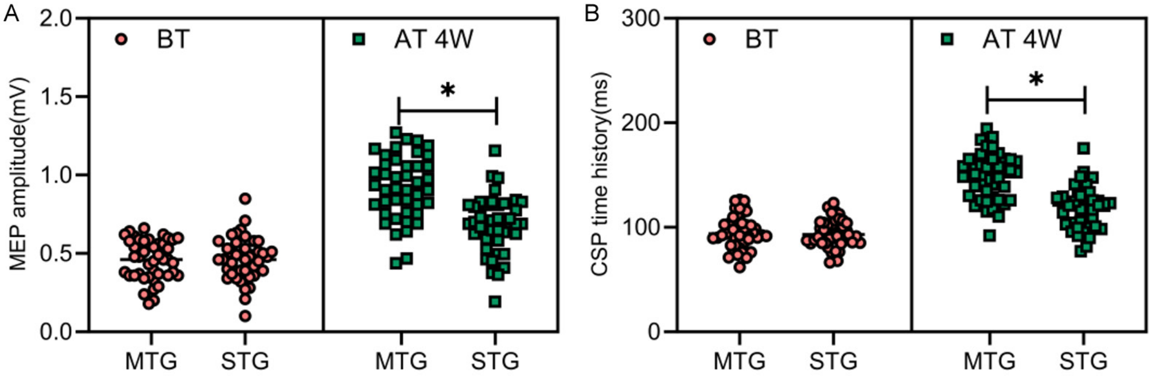

Figure 4. Comparison of cortical excitability indicators between the two groups. Pre-treatment MEP amplitude (A) and CSP duration (B) did not differ markedly between the two groups (P>0.05). After 4 weeks, the MTG demonstrated significantly greater MEP amplitude (A) and longer CSP duration (B) than the STG (P<0.05). Note: CSP: cortical silent period; MEP: motor evoked potential; MTG: multi-target stimulation group; STG: single-target stimulation group. $^{**}P<0.01$; $^{***}P<0.001$. n=43.

further supporting the arousal advantage of multi-target stimulation [16, 17]. The α/δ ratio may serve as a useful indicator for predicting prognosis in patients with DOC. In this study, the α/δ ratio was markedly increased in the MTG. The finding suggests that multi-target stimulation may improve the long-term prognosis in patients; however, its efficacy needs further investigation.

Effect of multi-target TMS on cortical plasticity

Cortical plasticity is an important mechanism for the brain to adapt to environmental changes and repair injuries. In this study, cortical excitatory and inhibitory functions were assessed using MEP amplitude and CSP duration. In the MTG, the results showed a marked increase in MEP amplitude and prolonged CSP duration, indicating improved cortical excitatory and inhibitory regulatory functions. MEP amplitude reflects the excitability of the corticospinal pathway, and its increase indicates enhanced excitability of the motor cortex and corticospinal pathway. CSP duration primarily reflects cortical GABAergic inhibitory function, and its prolongation indicates recovery of inhibitory function [18, 19]. Normal cortical function depends on the dynamic balance between excitability and inhibition. The changes in cortical plasticity observed in this study suggest that multi-target TMS may promote the restoration of this balance [20]. These effects may be

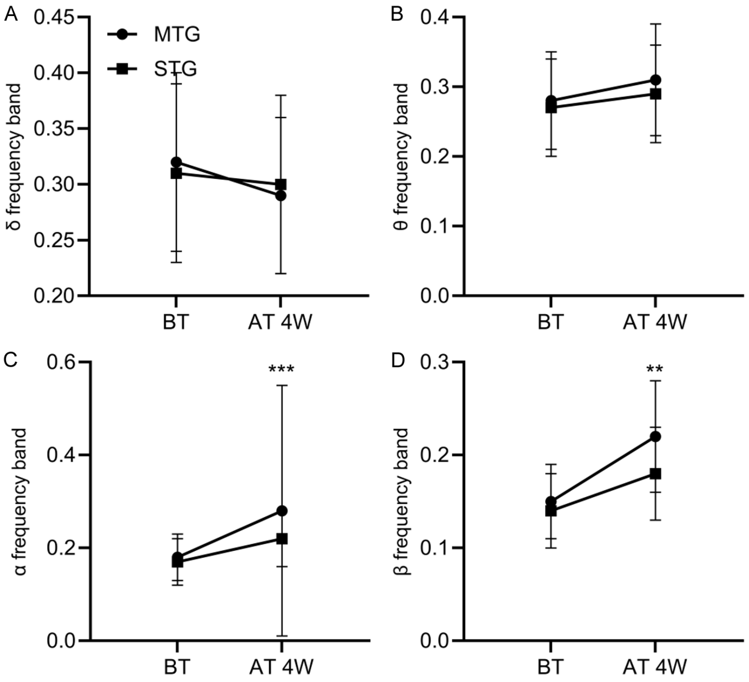

Figure 5. Comparison of brain functional connectivity indicators between the two groups. Both groups showed no marked difference in PLI values across frequency bands before treatment (P>0.05). After 4 weeks, the MTG exhibited significantly higher frontal-parietal PLI values in α and β frequency bands than the STG (P<0.05). Note: MTG: multi-target stimulation group; PLI: phase lag index; STG: single-target stimulation group. $^{**}P<0.01$; $^{***}P<0.001$. n=43.

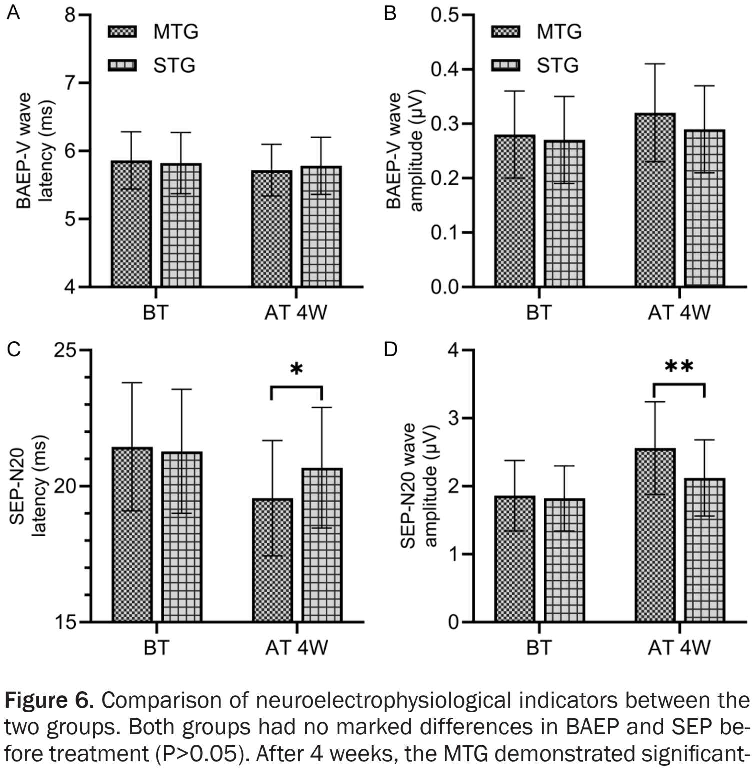

Figure 6. Comparison of neuroelectrophysiological indicators between the two groups. Both groups had no marked differences in BAEP and SEP before treatment (P>0.05). After 4 weeks, the MTG demonstrated significantly shorter SEP-N20 latency and significantly greater SEP-N20 amplitude than the STG (P<0.05). Note: BAEP: brainstem auditory evoked potentials; MTG: multi-target stimulation group; SEP: somatosensory evoked potentials; STG: single-target stimulation group. $^{*}P<0.05$; $^{**}P<0.01$. n=43.

due to high-frequency stimulation of L-DLPFC enhancing cortical excitability via facilitation of glutamatergic neural transmission, while low-frequency stimulation of M1 may improve inhibitory function by modulating the GABAergic system. The synergistic effects of the multi-target stimulation may ultimately promote the optimization of cortical plasticity [21, 22].

Effect of multi-target TMS on brain functional connectivity

This study showed that after 4 weeks, the MTG exhibited markedly higher frontal-parietal functional connectivity strength in both α and β frequency bands than the STG. Frontal-parietal functional connectivity is one of the neural substrates of consciousness, and the integrity of this network is closely associated with the level of consciousness. Earlier studies have suggested that patients with DOC generally have impaired frontal-parietal functional connectivity, manifested as weakened long-range functional connectivity and decreased network integration function [23, 24]. The enhanced functional connectivity observed in this study suggests that multi-target TMS may promote the functional reconstruction of damaged neural networks. The underlying mechanism may involve the L-DLPFC and M1, which are located near the frontal and parietal lobes, respectively. Multi-target stimulation

Table 2. Comparison of incidence of adverse events between the two groups [n (%)]

Group	n	Headache	Dizziness	Local skin discomfort	Nausea	Epileptic seizures	Total incidence
Multi-target stimulation group	43	3 (6.98)	2 (4.65)	2 (4.65)	1 (2.33)	0 (0.00)	8 (18.60)
Single-target stimulation group	43	2 (4.65)	2 (4.65)	1 (2.33)	1 (2.33)	0 (0.00)	6 (13.95)
χ^2	-						0.340
P	-						0.560

of these regions may enhance local neural activity, facilitate information transmission in the frontal-parietal pathway, and strengthen functional coupling between networks [7, 25]. This finding provides network-level evidence for the arousal-promoting mechanism of multi-target stimulation and offers a basis for further optimization of stimulation targets.

Effect of multi-target TMS on neuroelectrophysiological indicators

Changes in BAEP and SEP were also observed in this study. The MTG showed significantly shorter SEP-N20 latency and greater SEP-N20 amplitude compared with the STG. SEP reflects the integrity of somatosensory afferent pathways. N20 components are primarily generated in the primary sensory cortex, and improvement in N20 suggests sensory cortex function recovery [26]. In this study, no marked differences were found in the BAEP indicators between the two groups. This may be due to the brainstem auditory pathway being less affected by the stimulation target. This finding indicates that multi-target TMS primarily acts on the cortex and intercortical connections, rather than brainstem pathways.

Safety of multi-target TMS

Regarding safety, the incidence of adverse reactions was 18.60% in the MTG and 13.95% in the STG, with no significant difference. All adverse reactions were mild and transient, and no serious adverse events, especially epileptic seizures, occurred. The findings indicate that multi-target TMS demonstrates good safety. Although multi-target stimulation increases the total number of daily pulses, it does not increase the risk of adverse events when safety guidelines are strictly followed and stimulation intensity is controlled.

Clinical implications and limitations

The findings of this study indicate that multi-target TMS has certain advantages in arousal therapy in patients with DOC. It may to some extent improve patients' levels of consciousness, enhance EEG activity, and promote cortical plasticity changes and brain functional network reconstruction. Clinically, although multi-target stimulation protocols increase operation time and complexity, they may reduce patients' long-term medical burden by improving the arousal-promoting effects and shortening the rehabilitation process, highlighting their clinical value.

This study does have some limitations. First, this study was a retrospective, single-center analysis with a limited sample size, and the generalizability of the findings requires further validation. Second, follow-up was limited to 4 weeks, and the long-term arousal-promoting effects remain unclear. Third, the study did not investigate the optimal stimulation parameters. The therapeutic effects of various target combinations and stimulation parameters remain to be explored. Multicenter randomized controlled studies with large samples should be conducted to further verify the effects of multi-target TMS and explore individualized stimulation protocols.

In conclusion, multi-target TMS (L-DLPFC combined with R-M1) for patients with chronic DOC improves consciousness levels, modulates EEG activity, enhances cortical excitability and inhibitory function, and promotes frontal-parietal functional connectivity. These findings indicate effective arousal promotion and a favorable safety profile, highlighting its clinical potential for arousal therapy.

Disclosure of conflict of interest

None.

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