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Repetitive Transcranial Magnetic Stimulation Targeting the Dorsolateral Prefrontal Cortex Promotes Recovery of Consciousness in Patients with Disorders of Consciousness: A Meta-Analysis of Randomized Controlled Trials

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INTRODUCTION

Review question / Objective Objective: This systematic review and meta-analysis aims to evaluate the efficacy and safety of rTMS targeting the DLPFC for patients with DoC. Specifically, we sought to (1) determine whether rTMS significantly improves recovery of consciousness as measured by CRS-R, (2) assess the influence of stimulation parameters (frequency, laterality) on treatment outcomes, and (3) identify sources of heterogeneity such as patient characteristics, etiology, and concomitant therapies. By synthesizing the available RCT evidence, we aim to provide clinicians and researchers with evidence-based guidance on the therapeutic potential and limitations of rTMS in this challenging patient population.

Condition being studied Disorders of consciousness (DoC) are severe clinical syndromes that arise after acute brain injury and are characterized by impaired arousal and awareness. The main diagnostic categories include unresponsive wakefulness syndrome (UWS), also known as the vegetative state (VS), and the minimally conscious state (MCS). Patients in UWS/VS open their eyes and may display sleep–wake cycles but show no evidence of awareness of self or environment. In contrast, patients in MCS demonstrate minimal but reproducible signs of consciousness, such as visual tracking, following simple commands, or purposeful movements.

DoC typically occur following traumatic brain injury, hypoxic–ischemic encephalopathy, stroke, or intracerebral hemorrhage. Prognosis is often poor, with high rates of long-term disability and dependence on full-time care. Conventional treatments are limited, with pharmacological agents such as amantadine being the only medication consistently shown to accelerate recovery in this population. Other drugs (e.g., zolpidem, baclofen, dopaminergic agents) and standard rehabilitation interventions have shown inconsistent or modest effects.

The chronic and fluctuating course of DoC makes therapeutic interventions particularly challenging. Misdiagnosis rates can be high, sometimes up to 40%, due to the subtle behavioral signs that distinguish MCS from UWS. Reliable assessment therefore requires standardized tools such as the Coma Recovery Scale–Revised (CRS-R). Even with careful diagnosis, treatment outcomes vary greatly depending on etiology, disease duration, comorbidities, and residual brain network integrity.

In recent years, non-invasive neuromodulation techniques have emerged as promising options for DoC. Among these, repetitive transcranial magnetic stimulation (rTMS) has attracted attention for its ability to modulate cortical excitability and promote neural plasticity. By targeting frontal and parietal brain networks, rTMS may facilitate the recovery of consciousness-related functions. However, evidence from clinical trials remains heterogeneous, and its role in routine care has not yet been clearly established.

Given the devastating impact of DoC on patients, families, and healthcare systems, clarifying the therapeutic potential of rTMS is of high clinical and scientific importance.

METHODS

Participant or population This review will focus on adult patients (≥18 years) diagnosed with disorders of consciousness (DoC), including unresponsive wakefulness syndrome (UWS)/ vegetative state (VS) and the minimally conscious state (MCS). Eligible participants are those whose DoC developed following severe traumatic brain injury, hypoxic–ischemic encephalopathy, stroke, or intracerebral hemorrhage.

We will include studies in which the diagnosis of DoC was established using standardized clinical criteria and, whenever available, validated assessment tools such as the Coma Recovery Scale–Revised (CRS-R). Patients must have a stable clinical condition at baseline, defined as no rapid changes in level of consciousness due to acute medical or surgical complications.

No restrictions will be applied with respect to sex, ethnicity, or duration of DoC, but these variables will be extracted and considered for subgroup analyses. Pediatric populations (<18 years), patients with progressive neurodegenerative diseases, and those without a formal diagnosis of DoC will be excluded.

Intervention The intervention of interest is repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique that delivers repeated magnetic pulses through a coil placed over the scalp to modulate cortical excitability and neural network activity.

For the purpose of this review, we will specifically evaluate conventional high-frequency rTMS protocols (≥5 Hz, typically 10–20 Hz) applied to the dorsolateral prefrontal cortex (DLPFC) in patients with disorders of consciousness (DoC). Eligible interventions include rTMS administered as a stand-alone therapy or in combination with standard rehabilitative care, provided that stimulation parameters (frequency, intensity, number of sessions) are clearly reported.

Other neuromodulation modalities such as theta-burst stimulation (TBS), transcranial direct current stimulation (tDCS), or invasive techniques (e.g., deep brain stimulation) will be excluded. Similarly, studies targeting brain regions outside the DLPFC will not be considered, in order to reduce heterogeneity and allow a focused assessment of rTMS effects on recovery of consciousness.

Comparator The comparator interventions will include sham rTMS or placebo stimulation, in which identical procedures are applied but without delivering an effective magnetic field to the cortex. Sham stimulation may be delivered using an angled coil, a specially designed sham coil, or by producing similar acoustic and tactile sensations without active cortical stimulation.

In addition, studies in which the control group receives standard medical management and rehabilitation care alone (without active rTMS) will also be eligible. This ensures that the effects of rTMS can be evaluated relative to both sham stimulation and usual care.

Comparisons between different active rTMS protocols (e.g., high-frequency vs. low-frequency) will not be the primary focus but, if available, such data will be extracted and analyzed descriptively.

Study designs to be included This review will include randomized controlled trials (RCTs) with a parallel-group design that evaluate the effects of rTMS on patients with disorders of consciousness. Cross-over trials, case reports, case series, observational studies, conference abstracts, reviews, and non-randomized studies will be excluded to ensure methodological rigor and minimize bias.

Eligibility criteria In addition to the PICOS framework, we applied the following criteria:

Inclusion: Studies reporting pre- and post-intervention CRS-R scores or sufficient data to calculate effect sizes; patients receiving stable pharmacological treatment for ≥2 weeks prior to enrollment.

Exclusion: Non-English publications; studies lacking full-text availability; duplicate datasets; trials with incomplete rTMS protocol details (e.g., missing frequency, intensity, or stimulation site); studies involving pediatric populations (<18 years) or progressive neurodegenerative diseases; and interventions combining rTMS with other experimental neuromodulation techniques where the independent effect of rTMS could not be determined.

Information sources We will perform a comprehensive search of multiple electronic databases to identify all relevant randomized controlled trials evaluating repetitive transcranial magnetic stimulation (rTMS) in patients with disorders of consciousness. The following databases will be searched from inception to the latest update prior to analysis: PubMed/MEDLINE, Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus.

To ensure thorough coverage, we will also search clinical trial registries such as ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the Chinese Clinical Trial Registry (ChiCTR) for ongoing or unpublished trials.

In addition, we will review the reference lists of all included articles and relevant reviews to identify further eligible studies. If necessary, we will contact study authors to obtain additional data or clarification on study details not clearly reported in the published manuscripts.

Grey literature will be explored by searching conference proceedings, dissertations, and relevant organizational websites, although abstracts without sufficient methodological or outcome data will not be included in the quantitative synthesis. No restrictions will be placed on publication year. Only studies published in English will be considered due to feasibility constraints.

This multi-source approach aims to minimize publication bias and maximize the completeness of the evidence base for the planned systematic review and meta-analysis.

Main outcome(s) The primary outcome of this review will be the change in consciousness level as assessed by the Coma Recovery Scale–Revised (CRS-R), comparing pre-intervention and post-intervention scores between rTMS and control groups. When available, effect sizes (mean difference or standardized mean difference with 95% confidence intervals) will be calculated.

Secondary outcomes will include:

Post-treatment absolute CRS-R scores, allowing evaluation of the clinical state after the intervention.

Responder rates, defined as the proportion of patients demonstrating clinically meaningful improvement in CRS-R scores.

Subgroup effects, such as stimulation frequency (10 Hz vs. 20 Hz), laterality (left, right, or bilateral DLPFC), and etiology (traumatic vs. non-traumatic).

Safety and tolerability outcomes, including the incidence of adverse events such as headache, scalp discomfort, seizures, or treatment discontinuation.

Timing: Outcomes will be assessed at the end of the active treatment period (short-term effects). When available, we will also extract follow-up data beyond the treatment window to evaluate the durability of rTMS effects over time.

This outcome framework will allow us to quantify the efficacy of rTMS for recovery of consciousness, assess heterogeneity related to stimulation protocols and patient characteristics, and determine the safety profile of rTMS in this vulnerable population.

Quality assessment / Risk of bias analysis Quality Assessment of Primary Studies

The methodological quality and risk of bias of all included randomized controlled trials (RCTs) will be independently assessed by two reviewers using the Cochrane Risk of Bias tool (RoB 2.0). This validated framework evaluates potential sources of bias across five domains:

Randomization process (e.g., adequacy of sequence generation and allocation concealment);

Deviations from intended interventions (e.g., blinding of participants and personnel);

Missing outcome data (e.g., attrition and handling of incomplete data);

Measurement of the outcome (e.g., blinding of outcome assessors and reliability of CRS-R scoring);

Selection of the reported results (e.g., selective outcome reporting or protocol deviations).

Each domain will be rated as "low risk," "some concerns," or "high risk of bias." An overall risk of bias judgment will then be assigned for each study. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer if necessary.

In addition to the Cochrane tool, we will assess reporting quality and methodological transparency by checking for trial registration, ethical approval, and completeness of intervention reporting (e.g., stimulation parameters, duration, laterality). Sensitivity analyses will be conducted to explore whether excluding studies with high risk of bias alters the overall findings.

The results of the quality assessment will be presented in both tabular and graphical formats, allowing readers to visualize the distribution of risk of bias across studies and domains. This rigorous assessment will ensure that the conclusions of the review are based on evidence of the highest possible methodological quality.

Strategy of data synthesis Data will be analyzed using Review Manager (RevMan) and Stata software. For continuous outcomes (e.g., CRS-R score changes), effect sizes will be expressed as mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI). For dichotomous outcomes (e.g., responder rates, adverse events), risk ratios (RR) with 95% CI will be calculated. When trials report median and interquartile ranges, we will estimate means and standard deviations using validated statistical methods.

Meta-analysis will be performed using a random-effects model, given the expected heterogeneity in study populations and rTMS protocols. A fixed-effects model will be applied in sensitivity analyses to assess the robustness of findings.

Heterogeneity across studies will be quantified using the I^2 statistic (with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity) and Cochran's Q test ($p < 0.10$ considered significant). If substantial heterogeneity is detected, potential sources will be explored through subgroup and sensitivity analyses.

Subgroup analysis Subgroup analyses will examine whether treatment effects differ according to:

Stimulation frequency (10 Hz vs. 20 Hz);

Laterality of stimulation (left, right, bilateral DLPFC);

Etiology of DoC (traumatic vs. non-traumatic);

Duration of DoC (subacute vs. chronic).

Sensitivity analysis Sensitivity analyses will be conducted by excluding studies judged to have a high risk of bias, studies with small sample sizes, or those with incomplete outcome reporting, to evaluate the stability of results.

Where data from ≥10 trials are available, publication bias will be assessed using funnel plots and Egger's regression test.

If quantitative synthesis is not feasible due to heterogeneity or insufficient data, a narrative synthesis will be provided. All analyses will adhere to the PRISMA guidelines to ensure transparency and reproducibility.

Country(ies) involved China.

Keywords repetitive transcranial magnetic stimulation (rTMS); disorders of consciousness (DoC); Coma Recovery Scale–Revised (CRS-R); dorsolateral prefrontal cortex (DLPFC); meta-analysis; randomized controlled.

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