Effect of Individualized Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients With Disorder of Consciousness

Title	Effect of Individualized Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients With Disorder of Consciousness
Application	Department of Rehabilitation, Zhujiang Hospital, Southern Medical University
Purpose	Primary objectives: To examine whether individualized rTMS is more effective to improve CRS-R scores in DoC patients than the rTMS-sham control. Secondary objective : (1)To examine whether individualized rTMS is more effective to improve relative spectral power of EEG in DoC patients than the rTMS-sham control; (2)To examine whether individualized rTMS is more effective to improve functional connectivity of EEG in DoC patients than the rTMS-sham control; (3)To evaluate the safety of rTMS in DoC patients.
Research hypothesis	rTMS applied on the Individual-targeted selection area will improve DOC patients' level of consciousness
Design	Exploratory single-center, cross-over, double-blind, randomized controlled trial
Sample size	This is a crossover pilot study. The CRS-R total score after two-stage treatments will be considered as the primary efficacy outcome, while high-density EEG analysis (relative spectral power and functional connectivity) will be the secondary outcome. In this context[1], the sample size calculation will be based on an expected difference between the treatment groups of 20%, setting a significance level of 0.05% and a power of 80%. Considering patients' compliance and approximately 20% dropout rate during the study, the final sample size of 30 participants is needed. We consider this is an achievable sample size and adequate to allow for the dropout rate while still leaving a reasonable final sample.
Eligibility	Inclusion Criteria: 1) acquired brain injuries less than 1 year and more than 28 days in DOC; 2) no medical history of neuropsychiatric diseases; 3) no contraindications for rTMS or EEG, no sedatives in use or other drugs that might interfere with brain stimulation, such as Na+ or Ca2+ channel blockers or NMDA receptor antagonists; 4) stable state of disease and vital signs; 5) the families of the patients volunteered the patient to participate in the study and provided signed informed consent; 6) the integrity of the individualized stimulation target cortex are verified by MRI.Exclusion criteria: Exclusion Criteria:

	1) patients in other non-invasive or invasive neuroregulation trials; 2) motor evoked potential (MEP) in M1 region cannot be induced by TMS pulse; 3) uncontrolled epilepsy, seizure within 4 weeks before enrollment; 4) metallic implant in the skull, pacemaker, craniotomy under the stimulated site, implanted brain device.
Major interventions	10Hz rTMS
Evaluating indicator	Primary outcome: The Coma Recovery Scale-Revised (CRS-R), a total of 23 points, is widely used to define the level of consciousness and assess neurobehavioral recovery of patients with DOC. It is based on six subscales that assess auditory (4 points), visual (5 points), motor (6 points), motor/speech (3 points), communication (2 points), and arousal processes (3 points). Each item of CRS-R is in good agreement with the diagnostic and differential diagnostic criteria of VS/UWS, MCS and EMCS. The higher scores mean a better outcome. Secondary outcome: EEG will be acquired from 66 channels with positions of the International 10-20 System for 10 mins. The relative spectral power (RSP) and functional connectivity (FC) of participants will be calculated by the selected artifact-free EEG epochs at five frequency bands: δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), β (13-30 Hz), and γ (30-45 Hz). The investigators will compute off-line analysis to calculate RSP and FC.
Statistical method	Statistical hypothesis: Parametric hypothesis test 1. Group mean CRS-R scores before and after active/sham rTMS were analyzed by ANOVA with a two-stage crossover design; 2. The relative spectrum power and coherence before and after active/sham rTMS were analyzed by ANOVA with a two-stage crossover design; 3. If the overall means were unequal across each group, pairwise comparisons were performed using the SNK-q test; 4. Select the channel of interest at the average level of the active/sham rTMS group, extract the relative spectrum energies of each frequency band, and use the paired-sample t-test to compare the differences between the relative spectrum energies of the two groups; 5. Pairwise channel coherence was calculated along each channel at the mean frequency band of active/sham rTMS group using the paired sample t-test to compare the differences between the specific channel coherence of the two component pairs; Non-parametric test was used if the normal distribution is not satisfied. Effectiveness test: The efficiency test adopts the 2 test of paired R x C contingency table data. If the sample size is <40 or T <1, the Fisher exact probability method of four table data is used;

#**Table 1** Schematic timeline of the study

TIMEPOINT	Enrollment	Allocation	Post-allocation					Close-out
	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Enrolment	×							
Eligibility screen	×							
Informed consent	×							
Demographic information[1)]	×							
Medical history[2)]	×							
Vital signs[3)]	×			×		×		
Randomization		×						
Allocation		×						
Interventions								
Active rTMS			×		Washout		×	
Sham rTMS			×		Washout		×	
Assessments								
CRS-R[4)]	×			×		×		×
EEG recording[5)]	×			×		×		×
Adverse events			×	×	×	×	×	×

1) Demographic information includes the patients date of birth, sex and race;

2) Medical history includes DoC resulting from brain injury and other clinically significant past and present medical history;

3) Vital signs include blood pressure, pulse rate, respiration and body temperature;

4) CRS-R: Coma Recovery Scale-Revised;

5) EEG: Electroencephalogram.

Reference：

[1] Steven-A Julious. Sample size of 12 per group rule of thumb for a pilot study[J]. Pharmaceutical Statistics, 2005, 4(4): 287-291.