



Study Protocol and Statistical Analysis Plan

Study of Cerebral Structural and Functional Reorganization of Stroke Patients After Repetitive Transcranial Magnetic Stimulation (rTMS) Using the Method of Neuroimaging Brain Network Analysis

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Background: Many methods have been applied to facilitate recovery after stroke. However, improvement in rehabilitation strategies is necessary because many patients remain disabled after treatment^{1, 2}. Traditional methods, such as physical therapy and occupational therapy, are time-consuming and labor-intensive. Repetitive transcranial magnetic stimulation (rTMS) has been increasingly used for the treatment of depression, motor dysfunction after stroke, aphasia, and mental disorders since 2000^{3,91}. It is particularly popular in research studies on functional recovery and brain reorganization after stroke. Currently, the internationally recognized strategy is high-frequency (≥ 5 Hz) rTMS applied to the ipsilesional primary motor cortex (M1) to facilitate its reperfusion and reorganization¹⁰⁰. It has been proven to play a positive role in functional rehabilitation after stroke, and brain reorganization has been noted on functional magnetic resonance imaging (fMRI)^{9, 111}. However, low-frequency rTMS applied to the contralesional M1 may also facilitate recovery as it weakens the contralesional hemisphere's inhibitory effect on the ipsilesional hemisphere¹²¹. Some studies have used measurements, including clinical assessment, fMRI, motor evoked potentials (MEPs), and central excitatory time, to compare the two types of rTMS and have found no significant differences^{113, 141}. Many studies have demonstrated the positive role of rTMS in functional improvement, although these studies have varied in observation time and stages of stroke^{115, 161}. However, the onset and maintenance time of rTMS remain uncertain.

In this study, we aimed to evaluate the effectiveness of rTMS on motor rehabilitation after stroke using a longitudinal, prospective and randomized study, and to explore the central mechanism of rTMS in motor recovery after ischemic stroke through multimodal functional magnetic resonance imaging.

Methods:

Subjects

Patients aged 35-80 years, admitted to the Department of Peking Union Medical College Hospital between January 2013 and December 2018 for first onset of acute ischemic stroke will be included in this study. The study will be performed in accordance with the guidelines of the latest version of the Declaration of Helsinki. Subjects will be given written information and a verbal explanation concerning the study prior to obtaining consent for their participation.

Inclusion Criteria

The main inclusion criteria are: 1) stroke patients within 1 week after onset with unilateral cerebral subcortex lesion in the middle cerebral artery territory detected by diffusion weighted image (DWI), 2)

right-handed, 3) without memory loss or intelligence disorder, 4) never suffered stroke before.

Exclusion Criteria

The following patients will be excluded from the study: 1) direct damage to the cerebral cortex, a history of cerebral vessel disease, 2) tendency to hemorrhage or existed brain hemorrhage, 3) epilepsy or other mental disorders, 4) any MRI contraindications.

Grouping and Evaluation

The patients were divided into a real rTMS treatment group and a sham group randomly. A random number was generated by a computer, and the processing method was placed into a sealed envelope. A nurse who was not involved in the clinical evaluation was responsible for issuing and registering the number. The functional scores of the patients were independently assessed by an experienced neurologist at each follow-up time point. The staff members who implemented rTMS were not involved in the clinical assessment, and the rehabilitation physician was not aware of the patient groupings.

The scoring methods included the following: 1) National Institutes of Health Stroke Scale (NIHSS), 2) Barthel Index (BI), 3) Fugl-Meyer Assessment Upper Limb/Lower Limb (FMA-UL/LL), 4) modified Rankin Score (mRS), 5) the resting motor threshold (MT) of the hemiplegic upper limbs. The former 3 scores were the primary endpoints, and the latter 2 scores were the secondary endpoints. We evaluated each patient at 6 time points, including grouping time, the second day after treatment, 1 month after onset, 3 month after onset, 6 month after onset, and 1 year after onset.

rTMS

The MT (motor threshold) of the ipsilesional and contralesional abductor digiti minimi muscles were determined for every patient before rTMS or sham rTMS to evaluate motor function for both cerebral hemispheres. The RMT was defined as the lowest intensity capable of eliciting at least 5 MEPs of 50 μ V peak-to-peak amplitude in 10 consecutive stimulations when single-pulse TMS was delivered to the contralateral cortex. If the minimum MEP amplitude could not be detected, then it was recorded as 100%. MTs for bilateral cerebral hemisphere were recorded.

All patients received consecutive 10-day rTMS or sham rTMS. We used a Medtronic MagPro type magnetic stimulation device (Medtronic, Minneapolis, MN, USA) and a figure-eight coil (MC-B70, Medtronic). Regarding the safety threshold suggested by the International Federation of Clinical Neurophysiology (IFCN) and related studies, our protocol used 5 Hz rTMS applied to the ipsilesional M1. The treatment involved 50 trains of 20 pulses with 2-second intertrain intervals daily. In the rTMS

treatment group, coils were placed tangent to the scalp, while in the sham group, coils were placed perpendicular to the scalp.

Statistical analysis: Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data are described using means and standard deviations and were compared using the Mann-Whitney *U* test. Enumeration data were compared using the Chi-square test. A *P* value < 0.05 means significant difference.

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