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Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients

Wei Yang [a,1], Tao-Tao Liu [a,1], Xiao-Bin Song [b], Yan Zhang [c], Zhao-Hui Li [d], Zhi-Hua Cui [a,*], Qian Hao [a,*], Hong Lei Liu [a], Chun Ling Lei [a], Jun Liu [b]

[a] Department of Ophthalmology, The First Hospital of Jilin University, Changchun 130021, China
[b] Department of Emergency Surgery, Jilin Province People's Hospital, Changchun 130021, China
[c] Department of Otorhinolaryngology, Head and Neck Surgery, The First Hospital of Jilin University, Changchun 130021, China
[d] Department of Ophthalmology, People's Hospital of Changchun City, Changchun 130021, China

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ABSTRACT

Objective: : In this study three different stimulation parameters of repetitive transcranial magnetic stimulation (rTMS) were tested to compare the efficacy of continuous theta burst stimulation (continuous TBS) for rehabilitation of unilateral spatial neglect (USN) in stroke patients.

Methods: : Carefully selected cohort of thirty-eight stroke patients were randomly assigned to three treatment groups (1 Hz group, 10 Hz group and continuous TBS group) and sham group. Intervention in patients in the treatment group consisted of rTMS, while patients in the sham group received pseudo-stimulation for two weeks. All patients were administered star cancellation and line bisection tests at 4 different time points of the study. Further, all study subjects in the three treatment groups and sham group underwent diffusion-tensor imaging (DTI) at the beginning and at the end of treatment to calculate fractional anisotropy (FA) and mean diffusivity (MD).

Results: : Among the three stimulation parameters, star cancellation and line bisection tests revealed significant differences in outcomes at the end of treatments and one month after the end of treatments, compared to beginning of the treatments. Importantly, continuous TBS group patients displayed the best curative effect, based on behavioral scoring, at one month after end of the treatments, followed by the 1 Hz group and 10 Hz group. DTI results showed a significant increase in FA and MD in superior longitudinal fasciculus, superior occipitofrontal fascicle and inferior fronto-occipital fasciculus on the left side, as well as the capsula external and inferior fronto-occipital fasciculus on the right side, in patients after continuous TBS. In addition, compared to the sham group, patients stimulated with continuous TBS exhibited a dramatic increase in FA in the left external capsule.

Conclusion: : Our study presents strong evidence that rTMS significantly improves neurocognitive functions in USN, with continuous TBS showing the best curative effect. Enhanced connections in the white matter tract network related to visual attention, as assessed by DTI, might be the potential mechanism for the observed recovery in USN using continuous TBS.

1. Introduction

Stroke is the third leading cause of death after cancer and heart disease, and accounts for approximately 12% of deaths annually worldwide. Stroke is characterized by a partial loss of brain function as a result of disruption in blood circulation in the brain [1]. Approximately, 85% of stroke-related deaths occur in under-developed and developing countries, and nearly 750,000 patients are newly diagnosed with stroke each year in the United States, with 1 in 20 deaths caused by stroke [2,3]. Stroke results in serious disabilities, significant financial burden, post-stroke depression and unilateral spatial neglect (USN) [4]. USN is defined as an inability to orient towards, respond to, or report on stimuli appearing in the contralesional visual hemispace [5]. USN occurs when the neural network controlling spatial representation and awareness, the parietal–frontal cortical–subcortical network, is damaged by right hemispheric lesion in the territory supplied by the middle cerebral artery [6]. USN is principally caused by damage to the right hemisphere, but may also results from damage to parietal lobe, frontal lobe, thalamus or basal ganglia [7]. Neglect is a disorder in which a lesion in a network node affects intra-hemispheric and inter-hemispheric connectivity [8,

* Corresponding authors at: Department of Ophthalmology, The First Hospital of Jilin University, No. 71 Xinmin Street, Changchun 130021, Jilin Province, China.
E-mail addresses: cuizhihua_2013@126.com (Z.-H. Cui), haoqian_0602@126.com (Q. Hao).
[1] Wei Yang and Tao-Tao Liu both as co-first author.

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9]). Posterior parietal lobe serves as a unique site for convergence of sensory inputs from visual, auditory, vestibular and somatosensory areas. In-turn, the posterior parietal lobe has extensive connections with premotor cortex, the frontal eye fields, the superior colliculus and the paralimbic areas [10]. USN originates from widespread reduction in the function of these parietal and frontal areas associated with damaged subcortical nuclei [11]. Current therapeutic strategies for USN include intensive training for visual scanning, sensory stimulation, central cueing and pharmacologic methods [12,13]. Repetitive transcranial magnetic stimulation (rTMS), particularly the continuous theta burst stimulation (continuous TBS), has shown promise in treatment of USN [14].

Transcranial magnetic stimulation (TMS) is a noninvasive stimulation of small brain areas using a high-intensity magnetic field generated by an electric current passing through an inductive coil [15]. The magnetic field strength and the on/off state is controlled by altering the current, therefore, TMS parameters can be tightly regulated. TMS pulses elicit transient depolarization of neurons. However, when these pulses are applied repetitively, known as repetitive rTMS, cortical excitability can be increased or decreased depending on the stimulation parameters [16]. As such, low-frequency rTMS (≤1 Hz) suppresses local neural activities, while high-frequency rTMS (≥10 Hz) has excitatory effects on cortical activity, likely by modulating neurotransmitters such as dopamine and gamma amino butyric acid (GABA) [17]. Stimulation using 1 Hz reduces corticospinal excitability (long-term-disability (LTD)-like effect), whereas 10 Hz increases long-term potentiation (LTP)-like effect [18]. In stroke patients, the use of low frequency rTMS over the unaffected posterior parietal cortex decreased USN for 6 weeks [19]. Low frequency rTMS alters the inter-hemispherical competition in neural networks associated with attention, which is advantageous in USN treatment to relieve the symptoms of neglect [20]. Theta burst stimulation (TBS) is a variant of rTMS, which is effective in altering cortical excitability [21]. TBS is classified into intermittent theta burst stimulation (iTBS) and continuous TBS based on the pattern of stimulation [22]. The iTBS influences motor-evoked potentials (MEPs), producing long-term potentiation (LTP), and continuous TBS induces prolonged depression of brain activity for up to one hour [23, 24]. Interestingly, continuous TBS sustains excitatory after-effects on motor cortex and cortical excitability, and elicits behavioral responses in humans depending on the network states before stimulation and the associated changes in network interactions following the stimulation [25,26]. Moreover continuous TBS requires lower stimulation intensity to produce longer-lasting after-effects compared to conventional low-frequency rTMS [27]. Use of continuous TBS over left posterior parietal cortex leads to considerable functional improvement of cognitive disorders in traumatic brain injury patients, suggesting that continuous TBS is capable of improving visuo-spatial attention [28]. Continuous TBS was successfully applied to non-motor cortical areas, which increased phosphene thresholds after stimulation of the visual cortex [29]. Koch et al. reported that a 2-week application of continuous TBS over left hemisphere posterior parietal cortex is effective in promoting recovery from USN in patients with subacute stroke [30]. Based on the idea that rTMS inhibits cortical excitability, we hypothesized that stimulation with low-frequency TMS in contralateral posterior parietal cortex of may improve symptoms of USN in stroke patients. The present study compares the therapeutic efficacy of three different rTMS parameters in USN patients to understand the changes in brain network leading to functional recovery and to identify optimal treatment methods for stroke recovery.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Department of Ophthalmology, the First Hospital of Jilin University. Written informed consents were obtained from all eligible patients and the entire study conformed to the guidelines of the Declaration of Helsinki [31].

2.2. Subjects

Patient inclusion criteria were: (1) patient age between 18–80; (2) first stroke patients (cerebral infarction or hemorrhage) confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and in recovery time within 60–180 days; (3) USN confirmed by line bisection test, star cancellation test or clinical examination; (4) patients without serious heart, lung, and kidney disease or epilepsy; (5) patients without metallic implant of diamagnetic substance; (6) patients and their family members signed the informed consent. Exclusion criteria were: (1) patients aged <18 or >80 years; (2) patients with subarachnoid hemorrhage, venous sinus thrombosis, reversible ischemic attacks, transient ischemic attack (TIA) or reversible ischemic attack; (3) patients with worsening condition, new-onset infarction or hemorrhage lesions; (4) GCS score <15; (5) patients with obvious aphasia, severe cognitive-communication disorders; (6) patients with family history of epilepsy, or epileptiform discharges as revealed by video-electroencephalography; (7) patients with impaired organ function or failure in heart, lung, liver, kidney or other vital organs, and life expectancy was less than half a year; (8) patients with previous history of claustrophobia and uncooperative during examination; (9) hemianopsia patients (diagnosed with perimetry); (10) patients or their family members did not consent to this study.

Thirty-eight stroke patients met the criteria and were randomly divided into 4 groups: the sham group (10 cases), 1 Hz group (9 cases), 10 Hz group (10 cases) and continuous TBS group (9 cases). Based on the classification of Edinburgh handedness, all patients were right-handed and no significant differences were observed in gender, age, duration of disease, education, stroke type and the location of stroke for patients in each group (all $P > 0.05$) (Table 1).

2.3. Therapeutic method

All patients received routine rehabilitation as follows patients underwent "one on one" Bobath treatment with a physical therapist; the job therapist trained patients for the following daily activities: sitting by the bed, conversion between bed and wheelchair, and eating with tableware; speech therapist conducted speech training for 3–4 h per day, 5 days a week for a total 8 weeks of treatment. The rTMS stimulation was administered using a rapid magnetic stimulator (Magstim Company) with a figure-of-eight coil, peak intensity of stimulation at 2 T and pulse duration of 250 s. Patients in the sham group were given pseudo-stimulation for 2 weeks. Stimulation position according to the International 10/20 System was: P3 site at the contralateral hemisphere, which is the body surface projection of posterior parietal cortex. The resting motor threshold (RMT) of each patient was determined before treatment, which is defined as the minimum stimulation intensity required evoking MEPs of more than 50 μV in at least five of 10 trials at rest to the nearest 1% stimulator output. Determination method: Ag-AgCI surface electrode was placed on the abductor pollicis brevis muscle belly of upper limb at the hemiplegic side and MEPs were recorded. The reference electrode was placed in the first joint of the thumb. Coil B surface of TMS was placed extensor digitorum communis at muscle resting state, the stimulus intensity increased from maximum intensity of 20% to 1%, until five in ten evoke MEPs showed an amplitude of more than 50 μV, and the value was recorded as the stimulation threshold of resting state. In this study, the stimulation intensity was 80% of RMT with continuous treatment for 2 weeks [32]. The stimulation parameter in 1 Hz group was 1 Hz and stimulus duration for each sequence was 8 s, repeated 82 sequences with a total of 656 pulse number. The stimulation frequency in the 10 Hz group was 10 Hz, with a total pulse number of 1000 and stimulation interval of 55 s [33]. Continuous TBS group parameter was: 801 pulses, in bursts of 3 pulses at