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Effects of Theta Burst Stimulation on Suprahyoid Motor Cortex Excitability in Healthy Subjects

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Background: Continuous theta burst stimulation (cTBS) and intermittent TBS (iTBS) are powerful patterns of repetitive transcranial magnetic stimulation (rTMS), with substantial potential for motor function rehabilitation post-stroke. However, TBS of suprahyoid motor cortex excitability has not been investigated. This study investigated TBS effects on suprahyoid motor cortex excitability and its potential mechanisms in healthy subjects.
Methods: Thirty-five healthy subjects (23 females; mean age = 21.66 ± 1.66 years) completed three TBS protocols on separate days, separated by at least one week. A stereotaxic neuronavigation system facilitated accurate TMS positioning. Left and right suprahyoid motor evoked potentials (SMEP) were recorded using single-pulse TMS from the contralateral suprahyoid motor cortex before stimulation (baseline) and 0, 15, and 30 min after stimulation. The SMEP latency and amplitude were analyzed via repeated measures analysis of variance.
Results: cTBS suppressed ipsilateral suprahyoid motor cortex excitability and activated the contralateral suprahyoid motor cortex. iTBS facilitated ipsilateral suprahyoid motor cortex excitability; however, it did not affect the contralateral excitability. iTBS eliminated the inhibitory effect caused by cTBS applied to the contralateral suprahyoid motor cortex. TBS had no significant effect on the latencies of bilateral SMEP. TBS effects on suprahyoid motor cortex excitability lasted a minimum of 30 min.
Conclusions: TBS effectively regulates suprahyoid motor cortex excitability. Suppression of excitability in one hemisphere leads to further activation of the corresponding contralateral motor cortex. iTBS reverses the inhibitory effect induced by cTBS of the contralateral suprahyoid motor cortex.

Introduction

Dysphagia is a severe disability after stroke, with an incidence that ranges between 30% and 70% [1]. Dysphagia has been associated with an increased risk of dehydration, malnutrition, aspiration pneumonia, and mortality [1–3]. Aspiration pneumonia is one of the major causes of death in dysphagic stroke patients [2]. Hyoid–throat complex movement forward and upward comprises the precondition for the opening of the upper esophageal sphincter (UES), which guarantees the safety and effectiveness of swallowing. Insufficient forward and upward movement of the hyoid–throat complex contributes to repeatedly occurring aspiration and aspiration pneumonia, whereas the suprahyoid muscles play an important role in the forward and upward movement of the hyoid–throat complex [4,5].

Traditional treatments for dysphagia have focused on behavioral exercises and compensatory strategies, such as bolus modification,

Abbreviations: AMT, active motor threshold; cTBS, continuous theta burst stimulation; DTI, diffusion tensor imaging; EMG, electromyography; FDI, first dorsal interosseous; fMRI, functional magnetic resonance imaging; LTD, long-term depression; LTP, long-term potentiation; MEPs, motor evoked potentials; MSO, maximum stimulator output; iTBS, intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; SMEP, suprahyoid motor evoked potential; UES, upper esophageal sphincter.

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swallow posture changes, and protective maneuvers [6]. Although these treatments can improve swallowing safety to some extent, they cannot promote recovery of the damaged swallow-related neural networks in dysphagic stroke patients [7]. Furthermore, a recent systematic review identified limited evidence to support the medical efficacy of common dysphagia therapies and interventions [8]. Thus, the development of novel effective rehabilitation treatments is urgently needed.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive stimulation technique with the capacity to modulate cortical excitability and has exhibited substantial potential in dysphagia treatment. The application of high-frequency rTMS to the affected hemisphere [9] or low-frequency rTMS to the intact hemisphere [10,11] induced an improvement in the swallowing function of unilateral stroke dysphagic patients. The potential mechanism may be related to re-balanced interhemispheric interactions because it has been demonstrated that an interhemispheric imbalance is evident in unilateral stroke dysphagic patients and it hinders motor function recovery in stroke patients [12–14]. However, the understanding of rTMS mechanisms is inadequate, as the swallowing function also improves via the application of high-frequency rTMS to the intact hemisphere [15]. To date, no standard rTMS treatment protocols have been developed because of insufficient understanding of rTMS mechanisms. Furthermore, patient tolerance to these traditional rTMS techniques is low because of the long stimulation time and strong stimulation intensity.

Theta-burst stimulation (TBS), including continuous TBS (cTBS) and intermittent TBS (iTBS), is a powerful pattern of rTMS, which rapidly regulates motor cortical excitability [16]. Compared with traditional rTMS, TBS produces a robust and long-lasting effect with a low intensity after only 20–190 s of application in humans. Thus, it represents a safe and good rTMS option for motor function rehabilitation in stroke patients. Moreover, it has been confirmed that TBS is beneficial to the recovery of paretic hand function and aphasia in chronic stroke patients [17,18].

However, few studies have examined the effects of TBS on the swallowing motor system. Mistry et al. [19,20] evaluated the effects of TBS on cortical properties in the human pharyngeal motor system, and the results indicated that only iTBS to the hemisphere with stronger pharyngeal projections induced increased responses in the contralateral weaker projection 60–90 min post-iTBS [19]. No significant cTBS effect was detected on the pharyngeal motor cortex [20]. Moreover, Mistry et al. reported limited TBS effects on the pharyngeal motor system. However, the effects of TBS on the suprahyoid motor cortex have not previously been investigated. Furthermore, no previous studies have used a neuronavigation system to facilitate an accurate TMS position. It has been established that the suprahyoid muscles were innervated by the bilateral motor cortex, which was thought to be in a state of interhemispheric balance. We hypothesized that when the motor cortex excitability of one hemisphere decreased, the motor cortex excitability of the other hemisphere would increase, and vice versa. Therefore, the present study aimed to identify the effects of neuronavigated TBS on suprahyoid motor cortex excitability and investigate its potential mechanisms in healthy subjects.

Materials and methods

Participants

Thirty-five healthy volunteers (23 females; age range = 20–28 years; mean age = 21.66 ± 1.66 years) participated in this study. All subjects were right handed according to the Edinburgh Handedness Inventory [21]. The exclusion criteria included a history of swallowing problems, epilepsy, or brain, ear, nose, or throat surgery; significant medical disorders; pregnancy; a cardiac pacemaker; metal in the head or eyes; or the use of medication that acts on the neuromuscular system. The experiments were approved by the clinical research ethical committee of the Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all participants prior to participation in the experiments.

Neuronavigation

The motor cortices of the suprahyoid muscles in each hemisphere were targeted with a TMS neuronavigation system (SofTaxic, E.M.S., Bologna, Italy) that used a graphic user interface and a three dimensional (3D) optical digitizer (NDI, Polaris Vicra, Ontario, Canada) to precisely position the coil over the cortical site. This approach enabled a high degree of reproducibility and accuracy throughout the experimental protocols. The procedure involved the computation of an estimated volume of head magnetic resonance images (MRIs) for all subjects because MRIs were unavailable. The estimated MRIs, which referred to the Talairach space, were calculated using a warping 3D procedure, which operated on a template MRI volume on the basis of a set of approximately 40–50 points digitized from the subject's scalp. The digitized points were used to compute a subsequent set of reference points that were analogous to a set of points pre-localized on the scalp of the template. The warping procedure was performed using these two corresponding sets of reference points [22,23].

Electromyographic (EMG) recordings

Suprahyoid muscle EMG responses were detected with two pairs of bipolar silver-silver chloride electrodes (Yiruide, Wuhan, China). Each pair was positioned on the suprahyoid muscle surface, 1 cm lateral to the midline. One pair was placed over the left suprahyoid muscles, and the other pair was placed over the right suprahyoid muscles. The interelectrode distance was 2 cm for each pair of electrodes, measured from the center of the electrodes [24]. A pair of electrodes was placed on the surface of the right (dominant hand in all subjects) first dorsal interosseous (FDI) in a belly-tendon montage. All electrodes were connected to an EMG recording system (Yiruide, Wuhan, China). The MEP signals were amplified and filtered with a bandpass set between 2 Hz and 10 kHz. The response signals were processed through a 50/60 Hz noise eliminator (Yiruide, Wuhan, China) to remove unwanted electrical interference. The MEP recordings were digitized with a sample rate of 100 kHz and stored for offline analysis, using data analysis software (Yiruide, Wuhan, China).

TMS

Magnetic stimulation was performed using a figure-of-eight coil (external loop diameters, 70 mm) connected to a Rui Chi magnetic stimulator (Yiruide CCY-IA, Wuhan, China), which produced a maximum stimulator output (MSO) of 3.0 Tesla. The stimulating coil was held tangentially to the skull with the coil handle pointing backwards and laterally 45° away from the anterior–posterior axis. The exact position was adjusted according to the results of the online neuronavigation, such that the coil wing center was oriented perpendicularly to the target point, to deliver the maximum magnetic power.

TBS

TBS was performed using a Rui Chi magnetic stimulator (Yiruide CCY-IA, Wuhan, China) connected to a figure of eight coil with a 70 mm outer diameter (MSO of 3.0 tesla). The magnetic stimulus