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ALTERATIONS OF THE AMPLITUDE OF LOW-FREQUENCY FLUCTUATION IN HEALTHY SUBJECTS WITH THETA-BURST STIMULATION OF THE CORTEX OF THE SUPRAHYOID MUSCLES

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Abstract—Theta burst stimulation (TBS) has emerged as a promising tool for the treatment of swallowing disorders; however, the short-term after-effects of brain activation induced by TBS remain unknown. Here, we measured the changes in spontaneous brain activation using the amplitude of low-frequency fluctuation (ALFF) approach in subjects who underwent different TBS protocols. Sixty right-handed healthy participants (male, $n = 30$; female, $n = 30$; mean age = 23.5 y) were recruited in this study and randomly assigned to three groups that underwent three different TBS protocols. In group 1, continuous TBS (cTBS) was positioned on the left hemisphere of the suprahyoid muscle cortex. For group 2, intermittent TBS (iTBS) was placed on the left hemisphere of the suprahyoid muscle cortex. Group 3 underwent combined cTBS/iTBS protocols in which iTBS on the right hemisphere was performed immediately after completing cTBS on the left suprahyoid muscle cortex. Compared to pre-TBS, post-cTBS showed decreased ALFF in the anterior cingulate gyrus (BA 32); post-iTBS induced an increase in ALFF in the bilateral precuneus (BA 7); and post-cTBS/iTBS induced a decrease in ALFF in the brainstem, and resulted in increased ALFF in the middle cingulate gyrus (BA 24) as well as the left precentral gyrus (BA 6). Compared the effect of post-TBS protocols, increased ALFF was found in left posterior cerebellum lobe and left inferior parietal lobule (BA 40) (post-cTBS vs post-iTBS), and decreased ALFF exhibited in paracentral lobule (BA 4) (post-iTBS vs post-cTBS/iTBS). These findings indicate that multiple brain areas involved in swallowing regulation after stimulation of TBS over the suprahyoid muscles. cTBS induces decreased after-effects while iTBS results in increased after-effects on spontaneous brain activation. Moreover, iTBS can eliminate the after-effects of cTBS applied on the contralateral swallowing cortex and alter the activity of contralateral motor cortex and brainstem. Our findings provide a novel evidence for the short-term effect of TBS on spontaneous brain activation.

Key words: repetitive transcranial magnetic stimulation, theta-burst stimulation, magnetic resonance imaging, low-frequency oscillations.

INTRODUCTION

Swallowing is an essential life-sustaining function. Historically, the central neural control of swallowing was believed to be almost entirely dependent on brainstem reflexive mechanisms, which are thought to play a crucial role in the planning and execution of safe swallowing (Torii et al., 2012); however, in recent years, with the development of brain imaging and noninvasive brain stimulation techniques, the notion that the bilateral cerebral system is involved in human swallowing is increasingly accepted (Kern et al., 2001; Martin et al., 2001; Doeltgen et al., 2015). Dysphagia has a huge impact on quality of life and is associated with malnutrition and aspiration pneumonia and results in high mortality (Doeltgen et al., 2015); however, efficient treatment options for dysphagia recovery are still limited. Recently, rehabilitation-based interventions have been proposed for the treatment of dysphagia (Cabib et al., 2016). A large number of studies have reported that repetitive transcranial magnetic stimulation (rTMS) could change the excitability of the swallowing-associated motor cortex and result in an improvement of swallowing function in

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Abbreviations: ALFF, amplitude of low-frequency fluctuations; ANOVA, analyzed with one-way analysis of variance; BOLD, blood-oxygen level dependent; cTBS, continuous TBS; FA, flip angle; FOV, field of view; FWHM, full-width at half maximum; iTBS, intermittent TBS; MEP, motor-evoked potential; rs-fMRI, resting-state fMRI; rTMS, repetitive transcranial magnetic stimulation; SNR, signal-to-noise ratio; TBS, theta burst stimulation; TE, echo time; TR, repetition time.

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unilateral post-stroke dysphagic patients (Khedr et al., 2009; Yang et al., 2012). These findings indicated that rTMS is an effective treatment to induce cortical plasticity after stroke (Khedr et al., 2009; Verin and Leroi, 2009). rTMS was believed to induce a lasting effect on cortical excitability at the site of stimulation and on remote sites that are functionally connected with the target region (Suppa et al., 2008). Furthermore, the newly proposed theta burst stimulation (TBS), a novel form of rTMS employing a lower intensity relative to conventional rTMS protocols, to increase or reduce cortical excitability in subjects for up to 60 min after the end of stimulation, became a promising tool for cortical reorganization after stroke (Huang et al., 2005). Interestingly, different patterns of TBS delivery have opposite effects on the synaptic efficiency of the stimulated cortex. Increased cortical excitability is primarily found with intermittent stimulation, e.g., intermittent theta-burst stimulation (iTBS), while a single uninterrupted stimulation such as continuous TBS (cTBS) tends to suppress cortical excitability (Gamboa et al., 2010; Rahnev et al., 2013). Recent studies detected alterations of the motor-evoked potential (MEP) on the pharyngeal muscles induced by TBS (Huang and Mouraux, 2015; Suppa et al., 2016); however, few studies have ever explored the effect of TBS on the motor cortex excitability of swallowing muscles (Gow et al., 2004). Moreover, little is known about the alteration of spontaneous neuronal activity following the application of different patterns of TBS on the swallowing cortex.

Recently, there has been much interest in exploring the neural substrates of the human brain using resting-state fMRI (rs-fMRI). Low-frequency (0.01–0.08 Hz) fluctuations (LFF) in rs-fMRI are considered to be physiologically important and closely related to spontaneous neural activities in the brain (Biswal et al., 1995; Fox and Raichle, 2007). There are a number of strategies that can be adopted for studying rs-fMRI. Among them, a newly proposed approach, known as low-frequency fluctuations (ALFF), aims to measure the amplitude of low-frequency oscillations (LFOs) quantitatively, was introduced to detect local blood-oxygen level dependent (BOLD) signal variation due to regional spontaneous activity (Zang et al., 2007). This method tests the whole-brain BOLD activity strength on a voxel-wise basis. Studies of rs-fMRI in healthy subjects have indicated that ALFF is able to identify physiological states of the brain (Yang et al., 2007; Zou et al., 2013). Furthermore, this method has been increasingly used to investigate spontaneous brain activity in patients with neural disorders including ADHD (Zang et al., 2007; Yang et al., 2011), schizophrenia (Huang et al., 2010), Alzheimer's disease (Wang et al., 2011), and MDD (Jiao et al., 2011; Wang et al., 2012); however, to our best knowledge, no study has used ALFF to examine the spontaneous activity alterations induced by TBS application on the swallowing cortex.

The suprahyoid muscles play an important role in the forward and upward movement of the hyoid-throat complex in the process of swallowing (Furukawa et al., 2000; Spek et al., 2008) and were frequently regarded as the target swallowing muscles for the treatment of patients with dysphagia (Hybels et al., 2001; Wichniak et al., 2011; Morgan et al., 2012). The aim of this work was to explore the spontaneous brain activity alterations induced by different TBS protocols applied on the cortex of the suprahyoid muscles. We hypothesized that cTBS and iTBS targeted to the suprahyoid muscles related brain cortex would result in opposite effects on spontaneous brain activity. Additionally, it was reported that the reduction of swallowing response time following the initial 'virtual lesion' induced by applying inhibitory TMS was reversed by the subsequent exciting TMS (Mistry et al., 2007). Another study found that contralesional hemispheric reorganisation was associated with spontaneous recovery of swallowing function following stroke (Hamdy et al., 1996). These results indicate the importance of interhemispheric balance for swallowing motor function. Given the cTBS placed on the left cortex of suprahyoid muscles could be used as 'virtual lesion' in the present study, we hypothesized that the subsequent iTBS on the contralateral motor cortex would alter the effect of cTBS. To test these hypotheses, we compared the spontaneous brain activity alterations induced by different patterns of TBS applied on the motor cortex of the suprahyoid muscles using the ALFF approach.

EXPERIMENTAL PROCEDURES

Participants

Sixty right-handed, young, healthy participants (male, $n = 30$; female, $n = 30$; mean age = 23.5 ± 4.4 years) were recruited from a local community through advertisements for this study. All of the volunteers were free of neurological and/or psychiatric disorders, any previous exposure to neuropsychiatric medications, previous swallowing disorders, or previous experience of enrollment in TMS and MRI studies. All the participants had no regular smoking or drinking tea. The subjects were randomly assigned to one of three groups consisting of different TBS protocols. The study was carried out on the afternoon of Saturday or Sunday from September to October in 2016. Written informed consent forms were obtained from all participants prior to participation. The study was approved by the local Medical Ethics Committee in the Guangzhou First People's Hospital of Guangzhou Medical University in China. All of the studies were conducted in accordance with the World Medical Association Declaration of Helsinki.

Transcranial magnetic stimulation

Focal TBS pulses were delivered using a figure-eight coil (outer diameter, 70-mm) connected to a Magstim super rapid stimulator (Yiruide medical equipment Co., Wuhan, China). A stereotactic on-line navigation system (Softaxi Optic, Canada, NDI) was used to guide the sites of cortical stimulation. The participants were seated comfortably in an armchair. The coil was attached to the subject's scalp and placed toward the hemisphere. Cortical stimulation intensity was