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Dynamic aftereffects in supplementary motor network following inhibitory transcranial magnetic stimulation protocols

Gong-Jun Ji[a,b], Fengqiong Yu[a], Wei Liao[c], Kai Wang[d,a,b,*]

[a] Laboratory of Cognitive Neuropsychology, Department of Medical Psychology, Anhui Medical University, Hefei 230000, China
[b] Collaborative Innovation Centre of Neuropsychiatric Disorder and Mental Health, Anhui Province 230000, China
[c] Center for Information in BioMedicine, Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China
[d] Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei 230000, China

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ABSTRACT

The supplementary motor area (SMA) is a key node of the motor network. Inhibitory repetitive transcranial magnetic stimulation (rTMS) of the SMA can potentially improve movement disorders. However, the aftereffects of inhibitory rTMS on brain function remain largely unknown. Using a single-blind, crossover within-subject design, we investigated the role of aftereffects with two inhibitory rTMS protocols [1800 pulses of either 1-Hz repetitive stimulation or continuous theta burst stimulation (cTBS)] on the left SMA. A total of 19 healthy volunteers participated in the rTMS sessions on 2 separate days. Firstly, short-term aftereffects were estimated at three levels (functional connectivity, local activity, and network properties) by comparing the resting-state functional magnetic resonance imaging datasets (9 min) acquired before and after each rTMS session. Local activity and network properties were not significantly altered by either protocol. Functional connectivity within the SMA network was increased (in the left paracentral gyrus) by 1-Hz stimulation and decreased (in the left inferior frontal gyrus and SMA/middle cingulate cortex) by cTBS. The subsequent three-way analysis of variance (site×time×protocol) did not show a significant interaction effect or "protocol" main effect, suggesting that the two protocols share an underlying mechanism. Secondly, sliding-window analysis was used to evaluate the dynamic features of aftereffects in the ~29 min after the end of stimulation. Aftereffects were maintained for a maximum of 9.8 and 6.6 min after the 1-Hz and cTBS protocols, respectively. In summary, this study revealed topographical and temporal aftereffects in the SMA network following inhibitory rTMS protocols, providing valuable information for their application in future neuroscience and clinical studies.

Introduction

Transcranial magnetic stimulation (TMS) is a well-established, noninvasive technique for neuromodulation that is widely used in basic neuroscience (Bergmann et al., 2016) and clinical (Lefaucheur et al., 2014) studies. Through repetitive (r)TMS, brain activity can be modulated for a period that outlasts the stimulation time. As such, rTMS has potential therapeutic effects for treating neurological and psychiatric disorders (Lefaucheur et al., 2014; Fox et al., 2014).

The modulatory capacity of rTMS can be influenced by various treatment parameters, particularly the frequency of stimulation and temporal structure of the paradigm. By stimulating the motor cortex, the aftereffects of different rTMS protocols can be estimated and compared based on motor-evoked potentials (MEPs). Both low-frequency stimulation (≤1 Hz) and continuous theta burst stimulation (cTBS) can decrease motor cortex excitability (Di Lazzaro et al., 2011), which is usually explained by the long-term depression (LTD) of synaptic activity. These two inhibitory protocols have been used to alleviate clinical symptoms of various movement disorders (Kamble et al., 2014), such as Tourette's syndrome (TS) (Le et al., 2013; Wu et al., 2014; Landeros-Weisenberger et al., 2015) and Parkinson's disease (PD) (Eggers et al., 2015; Chou et al., 2015; Shirota et al., 2013). However, optimizing protocol parameters and improving treatment efficiency require clarification of the mechanism underlying the effects of inhibitory rTMS on the SMA.

Recent studies have used resting-state functional magnetic resonance imaging (RS-fMRI) to detect functional changes following rTMS (Eldaief et al., 2011; Watanabe et al., 2014; Nettekoven et al., 2014; Mastropasqua et al., 2014; Cocchi et al., 2015; Valchev et al., 2015; Chen et al., 2013; Gratton et al., 2013; Andoh et al., 2015; Halko et al.,

* Corresponding author at: Department of Neurology, the First Affiliated Hospital of Anhui Medical University, 81 Meishan Rd., Hefei 230032, China.
E-mail address: wangkai1964@126.com (K. Wang).

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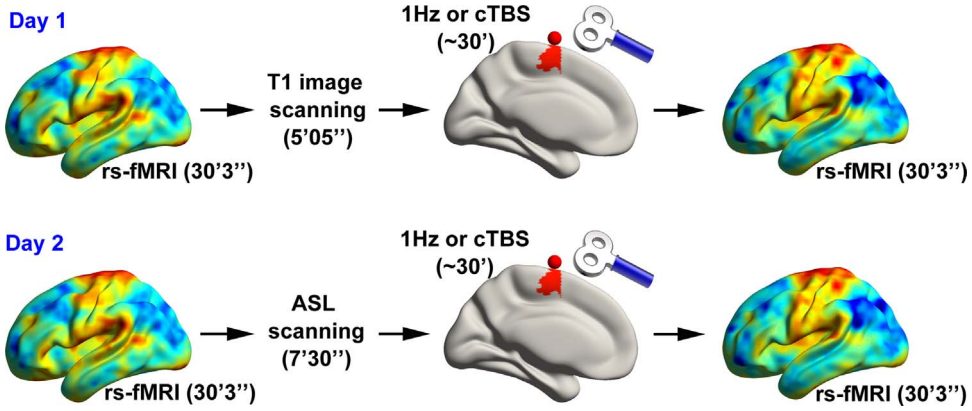

Fig. 1. Schematic of the experimental design. Using a within-subject design, each subject received cTBS and 1-Hz rTMS on 2 separate days (interval > 7 days) in a randomized order. The target area for real stimulation was defined as the superficial central point (MNI coordinates: −6, −6, 77; radius=6 mm) of the left SMA in the Automated Anatomical Labeling template. RS-fMRI datasets (30 min and 3 s) were acquired both before and after each rTMS session. T1 and arterial spin labeling (ASL) images were also acquired before rTMS sessions on the first and second days of the experiment.

2014). RS-fMRI is a relatively new but promising paradigm for investigating the functional architecture of the human brain (Zuo and Xing, 2014). Owing to the task-free feature, this paradigm is highly applicable in clinical practice, and has been used to detect abnormally functioning brain areas in various disorders with high spatial resolution (Ji et al., 2014; Liao et al., 2016a; Liao et al., 2016b). These studies were typically designed in a "measure-perturb-measure" manner. For example, increased functional connectivity was observed within the default mode network by comparing RS-fMRI datasets post- and pre-1-Hz rTMS in the posterior inferior parietal lobule (IPL) (Eldaief et al., 2011). In contrast, decreased functional connectivity was found in the motor and auditory networks after cTBS application in somatosensory (Valchev et al., 2015) and auditory (Andoh et al., 2015) cortices, respectively. This suggests that the modulatory effects of 1-Hz and cTBS stimulations may be achieved via distinct mechanisms, although both are inhibitory protocols. Additionally, the aftereffect of cTBS was more prominent than that of 1-Hz stimulation for both the decrease in MEP amplitude (Huang et al., 2005) and in terms of the duration of the aftereffects (Di Lazzaro et al., 2011). However, previous RS-fMRI studies only investigated functional alterations after rTMS within 10 min; it is therefore unknown how and when the system returns to baseline.

While SMA may be an effective target in inhibitory rTMS for alleviating symptoms of movement disorders (Le et al., 2013; Wu et al., 2014; Shirota et al., 2013), the underlying mechanism is unclear. Some RS-fMRI studies have investigated the aftereffects of rTMS in the motor network, but the target of stimulation in these studies was the primary motor or sensory area (Nettekoven et al., 2014; Valchev et al., 2015). In the current study, we combined rTMS and RS-fMRI to investigate the aftereffects of 1-Hz and cTBS protocols applied on SMA. In this single-blind, crossover-design study, we sought to identify regions mainly affected by these two protocols (topographical profile) and estimate the duration of the aftereffects (temporal profile).

Materials and methods

Subjects

We recruited 25 healthy, right-handed subjects with no history of neurological or psychiatric diseases. However, one of them left the city after the first day of the experiment; and five had excessive head motion at the start of scanning. Ultimately, only 19 subjects (sixm ales, mean age ± SD: 22.7 ± 2.1) completed the experiment. All subjects provided informed, written consent. The study was performed according to the Declaration of Helsinki (2008 revision) and approved by the local ethics committee.

Experimental design

We used a single-blind, crossover within-subject design (Fig. 1) to test the aftereffects of two inhibitory rTMS protocols (1Hzand cTBS) on (a) functional connectivity, (b) local activity, and (c) global properties of the SMA network. Each subject participated in two rTMS sessions on 2 different days at least 1 week apart to avoid carryover effects. The order of sessions was randomized between subjects. RS-fMRI datasets were acquired before and immediately after each rTMS session. We also acquired T1 and arterial spin labeling images before the rTMS session on the first and second experiment days, respectively. Diffusion-weighted images were acquired following the second RS-fMRI scan on the second day. All datasets were acquired at the Center for Cognition and Brain Disorders, Hangzhou Normal University, China.

Neuronavigated TMS

TMS was performed using a Magstim Rapid^2 stimulator (Magstim Company, Whitland, UK) coupled toa frameless stereotactic optical tracking neuronavigation system (Brainsight; Rogue Research, Montreal, Canada). High-resolution anatomical images were acquried (field of view=256×256 mm, slice thickness/gap=1/0 mm, in-plane resolution=256×256, repetition time=8.15 ms, echo time=3.18 ms, flip angle=8°, 176 sagittal slices) for neuronavigation. To measure the resting motor threshold (RMT), MEP amplitudes of the abductor pollicis brevis muscle were recorded using Ag/AgCl surface electrodes when the left "hand knob" area was stimulated witha 70-mm figure-eight coil (Magstim Company). The electromyography (EMG) signal was amplified, digitized, and displayed on a computer screen by the Rogue EMG device. RMT was defined as the lowest intensity evoking a small response (> 50 μV) in more than five of 10 consecutive trials, and was assessed before each rTMS session.

For the 1-Hz session, pulses were continuously delivered at 110% of the RMT at 1 Hz over 30 min (1800 pulses in total). The total number of stimulations was designed as per a previous RS-fMRI study using 1-Hz rTMS (Eldaief et al., 2011). The cTBS protocol lasted 40 s and consisted of a burst of three pulses delivered at 50 Hz, which was repeated every 200 ms (at 5 Hz) for a total of 600 pulses (Valchev et al., 2015; Huang et al., 2005). In the cTBS session, this 40-s protocol was repeated three times (1800 pulses in total) seperated by two 15-min breaks (controlled by a stopwatch). With this design, there was a similar interval between the two fMRI scans (~30 min) at 1-Hz and cTBS experiments. We hypothesized that in contrast to the negative findings in two-block cTBS (Gamboa et al., 2011), a three-block design would show cumulative aftereffects (Nettekoven et al., 2014; Volz et al.,