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Research article

Network-wise cerebral blood flow redistribution after 20 Hz rTMS on left dorso-lateral prefrontal cortex

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ABSTRACT

The repetitive application of transcranial magnetic stimulation (rTMS) on left dorsolateral prefrontal cortex (DLPFC) has been consistently shown to be beneficial for treating various neuropsychiatric or neuropsychological disorders, but its neural mechanisms still remain unclear. The purpose of this study was to measure the effects of high-frequency left DLPFC rTMS using cerebral blood flow (CBF) collected from 40 young healthy subjects before and after applying 20 Hz left DLPFC rTMS or SHAM stimulations. Relative CBF (rCBF) changes before and after 20 Hz rTMS or SHAM were assessed with paired-t test. The results show that 20 Hz DLPFC rTMS induced CBF redistribution in the default mode network, including increased rCBF in left medial temporal cortex (MTC)/hippocampus, but reduced rCBF in precuneus and cerebellum. Meanwhile, SHAM stimulation didn't produce any rCBF changes. After controlling SHAM effects, only the rCBF increase in MTC/hippocampus remained. Those data suggest that the beneficial effects of high-frequency rTMS may be through a within-network rCBF redistribution.

1. Introduction

Since the seminal work by Barker et al. [1] reporting that Transcranial Magnetic Stimulation (TMS) can modulate the neural activation in the targeted motor cortex, TMS has been rapidly developed into a widely used technique in neuroscience to explore human brain physiology by noninvasively stimulating brain nerve cells through the intact scalp [2]. While a single TMS pulse only produces short, rapidly changing magnetic field to induce electrical currents in underlying neurons and associated cortical tissue [3,4], the repetitive application of TMS (rTMS) has been shown to have more sustained effects on the excitability of the stimulated brain regions to either excite or suppress the cortical activity [5]. More importantly, accumulating evidence from human and animal studies showed that rTMS affects not only the stimulated site but also remote regions beyond the stimulation site, impacting a distributed network of brain regions [6–9]. These effects of rTMS are particularly beneficial from a therapeutic point of view, making rTMS a promising neuromodulational approach for treating various psychiatric and neurological diseases, such as major depressive disorder, schizophrenia, Parkinson's disease etc [10–12], which usually affect a widespread of brain regions.

Neuroimaging, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), can spatially resolve neuronal activity in the entire brain simultaneously, providing an ideal tool to examine the causal functional alterations and inter-regional interactions due to TMS in the entire brain [13–16,9,17,18,8,19–22]. The most widely used neuroimaging technique in TMS research is the blood-oxygen-level-dependent (BOLD) fMRI, which provides relatively high signal to noise ratio and temporal resolution compared to other MR measures. However BOLD signal is not quantitative, making it difficult to be directly compared across different scan days. Arterial spin labeling (ASL) perfusion MRI is a completely non-invasive approach for measuring the quantitative cerebral blood flow (CBF) (with a unit of measurement that refers to a physical quantity, ml/g/min) [23], providing a unique tool for assessing either the dynamic functional changes or the state (tonic) changes induced by TMS, and better comparability across scan sessions. But a combination of ASL and TMS still remains under explored with two papers found in Pubmed thus far [24,25]. Orosz et al. [25] found a significant increase of local CBF in the primary motor cortex after applying theta burst stimulation (TBS) on the right motor cortex, but not after SHAM stimulation (used for controlling the placebo effects). Gratton et al. [24] demonstrated that TBS-induced rCBF changes were related to TBS-induced changes in functional connectivity of the relevant intrinsic networks, and further suggested using

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CBF as a marker of individual differences in the effects of TBS.

In the present study, we applied rTMS in combination with pseudo-continuous arterial spin labeling (pCASL) in order to add to the inceptive TMS + ASL literature with findings of regional CBF changes in response to high-frequency rTMS on left DLPFC. Left DLPFC was chosen as the TMS target site because it is the most widely used one in the literature. Numerous evidence has demonstrated that DLPFC plays crucial roles in various attention-demanded cognitive tasks such as working memory and executive function [26], attention [27], decision making [28] and so on. Moreover, functional and structural studies indicated that DLPFC is connected to many cortical and sub-cortical regions, stimulating DLPFC can also provide a means to assess the remote effects of rTMS through network-wise interactions. Based on previous literature, we hypothesized that high-frequency rTMS would affect regional CBF not only in the stimulation site but also in brain regions which reside in the same networks as the stimulation site.

2. Methods

2.1. Participants

The study was approved by local internal review board and adhered to the Declaration of Helsinki. Forty healthy young adults (mean age: 22.73 ± 2.84years, 17 males), who gave written informed consent before participating in this study, were randomly divided into two groups: rTMS group or SHAM group. All subjects were right-hand and were naïve to TMS and had no history of psychiatric illness or neurological disorders. Subjects were instructed to refrain from caffeine, alcohol, nicotine or any kind of drugs for at least 24 h before the start of the experiment.

2.2. Experimental design

Each subject received two sessions of MRI scans which were performed on two separate days with 48 h apart using the same imaging protocol. Subjects received real rTMS or SHAM stimulation in only one session but no stimulation in the other. The order of having the stimulation or no-stimulation session was randomized and counterbalanced across subjects. The MRI scan after stimulation (rTMS or SHAM) was performed right after rTMS (post-rTMS) or SHAM stimulation (post-SHAM) (within 15 min due to the pre-scan preparations) to ensure that the stimulation effects are measured [9]. The 48 h interval between the two sessions was chosen to avoid any residual rTMS or SHAM effects from the preceding session if the stimulations were applied therein.

2.3. rTMS

During rTMS or SHAM procedure, the subjects were instructed to lie down in a chair with a pillar to support their heads. The rTMS or SHAM experiments were administrated using a Magstim TMS machine with a figure-of-eight coil (Magstim Inc, Sheffield). The stimulation site was located to be within the left DLPFC with a coordinate of [−40, 26, 37] in the Montreal Neurological Institute (MNI) space using the BrainSight navigation system (Rogue Research Inc).

rTMS was applied following the safety guidance provided by the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulator [29]. rTMS was administered in 12 successive pulse blocks interleaved with 28 s quite time. Each block consisted of 50 pulses with 20 pulses per second (20 Hz) for 2.5 s. The magnitude of pulse was set to be 90% of the resting motor threshold. The total experiment time was 5.63 min. For SHAM rTMS, parameters were set to be the same as the high frequency rTMS experiments except that the coil was placed at an angle of 90 ° to the skull. The target site was located at the same place for individual subjects in both rTMS and SHAM experiments, with the stimulation triggered on the platform of Magstim Rapid stimulator (Magstim Inc. Sheffield).

2.4. MRI data acquisition

MRI was performed twice for each group of subjects using the same scanning protocols on a 3T whole-body GE MR 750 Scanner (GE, Waukesha, USA) with a standard 8 channel receiver coil. During the scan, a comfortable and tight cushion was placed to immobilize the head and reduce motion. The participants were instructed to relax and remain still with their eyes open, not to fall asleep, and not to think about anything in particular. All subjects were monitored through the video camera in the scanner room and nobody was found to fall asleep during the scan, which was also confirmed by interview after the scan.

High-resolution T1-weighted structural MRI was acquired with a3Dspoiled gradient echo sequence (3D SPGR) with repetition time/echo time (TR/TE) = 8.1/3.39 ms, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1.0 mm^3 isotropic voxels, 176 slices without interslice gap. This image serving as an anatomical template for coregistration with ASL images.

CBF was measured with a GE product pCASL technique with 3D spiral data acquisition (label time = 1.45 s, delay time = 1.52 s, voxel size = 3.90 × 3.90 × 3.4 mm^3, TR/TE = 4.69 s/10.86 ms, acquisition excitation flip angle = 90°, refocusing pulse flip angle = 111°).

2.5. Imaging processing and statistical analysis

The CBF data preprocessing was done using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The CBF images were first co-registered to the structural MRI images, then warped to standard MNI space. To avoid the interference of global CBF fluctuations, the absolute CBF maps were converted into normalized relative CBF (rCBF) maps by equation: rCBF = (absolute CBF − GM_mean)/GM_mean, where absolute CBF is the CBF value at each voxel, GM_mean is the mean CBF within the grey matter. The rCBF maps were then smoothed with an isotropic Gaussian kernel with a full-width-at-half-maximum of 8 mm^3. The group analysis was performed using AFNI (http://afni.nimh.nih.gov/afni/) by employing paired T-test between conditions of with or without stimulation for each group. To further compare the rCBF changes caused by rTMS and SHAM conditions, the two sample T-test was performed between rTMS-induced rCBF changes and SHAM-induced rCBF changes of two subject groups.

3. Results

The global CBF with and without rTMS stimulation for the rTMS group were 55.99(± 9.89) and 56.20(± 7.67) ml 100 g^{-1} min^{-1}, respectively. For the SHAM group, the values were 55.38(± 10.97) and 55.49(± 11.51) ml 100 g^{-1} min^{-1} with and without SHAM stimulation respectively. No significant changes to the global CBF were observed between rTMS and SHAM.

Fig. 1A shows the brain regions with significant rCBF changes due to the rTMS stimulation (paired T-test, voxel-wise $p < 0.005$ (uncorrected), cluster size > 152 voxels (alpha < 0.05 using AlphaSim correction)). By contrast, no rCBF change was found for the SHAM group (Fig. 1B). For rTMS group, three cortical nodes were identified with rCBF changes, namely, left anterior medial temporal cortex (MTC)/hippocampus, precuneus and cerebellum. The mean rCBF was increased from 0.748 to 0.803 in left temporal gyrus, decreased from 1.139 to 1.089 and from 0.9956 to 0.9371 for precuneus and right cerebellum respectively.

To further identify the regional CBF differences caused by rTMS-induced and SHAM-induced rCBF changes, a two-sample T-test (voxel-wise $p < 0.005$ (uncorrected), cluster level $p < 0.05$ corrected with AlphaSim correction) was carried out between the rTMS and SHAM groups. Fig. 2 shows the results of rCBF change difference of rTMS after