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Stimulation of the Pre-SMA Influences Cerebral Blood Flow in Frontal Areas Involved with Inhibitory Control of Action

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ABSTRACT

Selection of the most appropriate response necessitates inhibition of competing or prepotent responses. It is important to characterize which cortical areas are relevant to achieve response inhibition. Using the stop signal task, previous imaging studies revealed consistent activation in the right pre-supplementary motor area (pre-SMA). However, imaging alone suffers from the limitation that it can only provide neuronal correlates and cannot establish causality between brain activation and behavior. Repetitive transcranial magnetic stimulation (rTMS) can be used to temporarily interfere with the function of a cortical area considered to play a specific role in the behavior. Thus, we combined rTMS with $H_2{}^{15}O$ positron emission tomography (PET) scans during the stop signal task, to test whether rTMS-induced changes in excitability of the right pre-SMA influenced response inhibition. We found that rTMS over the pre-SMA increased the efficiency of the inhibitory control over prepotent ongoing responses. A significant interaction was present in the left inferior frontal gyrus (IFG) along with an increase in regional cerebral blood flow (rCBF) in the left pre-SMA, left IFG, right premotor and right inferior parietal cortex. These areas best fitted the path analysis model in the effective connectivity model. The results of this study suggest that stimulation of the right pre-SMA, by interfering with its activity, may have a significant impact on response inhibition.

Introduction

Reactive inhibition, i.e., stopping an ongoing movement upon presentation of an external and sudden stimulus, relies on a rapid-acting circuit based on interactions between cortical and subcortical regions. The stop signal paradigm [1], which measures how accurately and rapidly a participant can inhibit an ongoing movement, shows altered performance in patients with focal lesions over the inferior frontal gyrus (IFG) [2] and the pre-supplementary motor area (pre-SMA) [3]. Functional magnetic resonance imaging (fMRI) studies depict these two areas as key players in response inhibition within a 'stopping' network that also involves the primary motor cortex (M1), inferior parietal cortex, subthalamic nucleus (STN), and striatum [4–10]. During successful and unsuccessful inhibition, the inhibitory network within the right hemisphere becomes active with the engagement of the pre-SMA and IFG [4] contributing to the magnitude of response inhibition. However, the extent of contribution of each area to inhibition in the stop signal is unknown. One study showed that participants with more efficient response inhibition had greater pre-SMA activation [11], suggesting that perhaps the pre-SMA is critically needed during successful inhibition. Another study, while emphasizing the importance of the pre-SMA and M1 connectivity (closely functionally related) in inhibiting a movement, also suggested that the IFG plays an important role in orienting participant's attention to adequately inhibit their response [10]. This was also supported by other experiments that showed the role played by the IFG in attention during inhibition and cue detection [12–14]. A recent meta-analysis performed on 21 studies investigating movement inhibition pointed to the functional relevance of the pre-SMA as a controlling area for adaptive behavior [15]. Thus, in the

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current study, we aim to test our hypothesis that the right pre-SMA is important for action inhibition by combining $H_2{}^{15}O$ positron emission tomography (PET) with continuous theta burst stimulation (cTBS).

Although neuroimaging studies can provide valuable information about the involvement of specific brain areas in response inhibition, it suffers from the limitation that it cannot determine a causal relation between observed brain activity and behavioral performance [16]. Thus, the specific functional relevance (active role vs. simple epiphenomenon) of those structures during response inhibition remains to be established.

Repetitive transcranial magnetic stimulation (rTMS) attempts to address this issue by temporarily modulating those cortical areas that are considered to play a specific role in the behavior [17]. rTMS is a non-invasive stimulation technique that exerts a temporary and reversible effect in the underlying cortex and distally interconnected brain areas [18,19]. Previous reports suggest that rTMS applied over the IFG or pre-SMA enhances or impairs response inhibition in healthy participants [20–24].

We set up three different experimental analyses. First, the behavioral effect of rTMS during the stop signal task was assessed, predicting that cTBS over the right pre-SMA would influence the efficiency of inhibitory control. Second, we combined cTBS with $H_2{}^{15}O$ PET during performance of the stop signal task, predicting that cTBS would affect regional cerebral blood flow (rCBF) in the neural network underlying response inhibition. Finally, we used a connectivity model approach to identify the critical neural interactions modulated by rTMS delivery relative to a sham condition.

Materials and methods

Participants

In the first experiment (i.e., TMS and behavior), we studied 16 right-handed healthy participants (8 men, mean age 26.5 ± 4.1; Edinburgh handedness inventory score 91%). Participants underwent TMS and stop signal task on two separate days. On one day, they performed the task with the right hand and the other day with the left hand. The latter was performed to rule out a potential TBS effect on the contralateral pre-SMA. Participants were excluded on the basis of history of psychiatric and/or neurological disorder, drug or alcohol abuse, pregnancy and migraine. Individual T1-weighted high-resolution MRI images were obtained to screen for structural lesions and TMS target localization. In the second experiment, 8 out of those 16 participants entered into an imaging session where rTMS was combined with PET (Fig. 1). This study was performed at least one week apart from the first behavioral experiment and completed during the same time of the day. The study protocol was approved by the Ethics Committee of the Center for Addiction and Mental Health Research, University of Toronto. Written informed consent was obtained from each participant before taking part in the study.

TMS procedure

A Magstim Rapid^2 Magnetic Stimulator (Magstim, UK; biphasic) was employed to apply TMS using a figure-of-eight coil (70 mm diameter). Stimulus intensities, expressed as a percentage of the maximum stimulator output, were set at 80% of the active motor threshold (AMT). AMT was defined as the lowest stimulus intensity able to elicit 5 motor evoked potentials (MEPs) of at least 50 μV of the contralateral first dorsal interosseus (FDI) muscle, averaged over 10 consecutive stimuli delivered over the right hand motor cortex (M1) at intervals longer than 5 s. During the determination of the AMT, participants were instructed to maintain a steady muscle contraction of 20% of maximum voluntary contraction. Right M1 was marked on the subjects' scalps to later apply sham TBS.

We used a protocol with three blocks (20 s each) of cTBS (see Fig. 1B); [25–27]. Blocks were separated by 1-min intervals. Each 20 s block consisted of 3 pulses at a rate of 50 Hz repeated every 200 ms (Fig. 1B); [28]. Overall, 300 trains with a total of 900 pulses were applied in each stimulation session. This off-line cTBS protocol produces a long-lasting (up to 60 min) influence limited to the underlying cortex [29,30] and is ideal for our TMS/PET experimental design. The right pre-SMA stimulation was applied with the coil handle placed tangentially to the midline and oriented in a lateral direction inducing the electrical current along the lateral-to-medial axis. The sham condition was delivered over the right hand M1 with the coil tilted 90° ensuring no active stimulation while using the same protocol of cTBS. cTBS was applied following safety guidelines [31,32].

In order to target the right pre-SMA, we used a procedure that takes advantage of the standardized stereotaxic space of Talairach and Tournoux [33] and frameless stereotaxy [34]. A high-resolution MRI (GE Signa 1.5 T, T1-weighted images, FSPGR with repletion time = 11.9 ms, echo time = 5 ms, flip angle = 40 mm, slice thickness = 1 mm, NEX = 1, matrix size = 256 × 192) of every

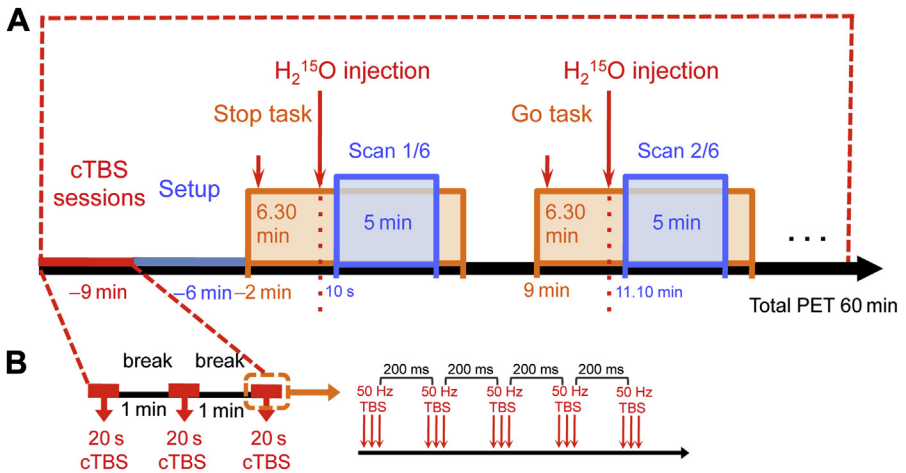

Figure 1. Experimental procedure combining cTBS with $H_2{}^{15}O$ PET. (A) Timeline of the TMS and $H_2{}^{15}O$ PET session. (B) Three cTBS blocks (20 s each) with one-minute break were applied prior the task.