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Functional MRI-navigated Repetitive Transcranial Magnetic Stimulation Over Supplementary Motor Area in Chronic Tic Disorders

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ABSTRACT

Background: Open label studies have shown repetitive transcranial magnetic stimulation to be effective in reducing tics.
Objectives: To determine whether 8 sessions of continuous theta burst stimulation (cTBS) over supplementary motor area (SMA) given over 2 days may reduce tics and motor cortical network activity in Tourette syndrome/chronic tic disorders.
Methods: This was a randomized (1:1), double-blind, sham-controlled trial of functional MRI (fMRI)-navigated, 30 Hz cTBS at 90% of resting motor threshold (RMT) over SMA in 12 patients ages 10–22 years. Comorbid ADHD ($n = 8$), OCD ($n = 8$), and stable concurrent medications ($n = 9$) were permitted. Neuronavigation utilized each individual's event-related fMRI signal. Primary clinical and cortical outcomes were: 1) Yale Global Tic Severity Scale (YGTSS) at one week; 2) fMRI event-related signal in SMA and primary motor cortex (M1) during a finger-tapping motor task.
Result: Baseline characteristics were not statistically different between groups (age, current tic/OCD/ADHD severities, tic-years, number of prior medication trials, RMT). Mean YGTSS scores decreased in both active (27.5 ± 7.4 to 23.2 ± 9.8) and sham (26.8 ± 4.8 to 21.7 ± 7.7) groups. However, no significant difference in video-based tic severity rating was detected between the two groups. Two-day post-treatment fMRI activation during finger tapping decreased significantly in active vs. sham groups for SMA ($P = 0.02$), left M1 ($P = 0.0004$), and right M1 ($P < 0.0001$). No serious adverse events occurred.
Conclusion: Active, fMRI-navigated cTBS administered in 8 sessions over 2 days to the SMA induced significant inhibition in the motor network (SMA, bilateral M1). However, both groups on average experienced tic reduction at 7 days. Larger sample size and protocol modifications may be needed to produce clinically significant tic reduction beyond placebo effect.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a method of noninvasive brain stimulation with therapeutic potential in neuropsychiatric conditions. Regulatory agencies in several countries have approved rTMS for the treatment of severe depression. Due to its potential clinical impact, researchers have been studying rTMS in other conditions, such as Tourette Syndrome (TS), for symptom reduction.

Since the first report of tic reduction by rTMS [1], several studies have shown rTMS to be effective in decreasing tics [2–6] while others demonstrated no benefit [7,8]. Both study design and stimulation parameters likely contribute to the mixed results. Open-label studies were more likely to show benefit [1–5] than sham-controlled and blinded studies [6–8]. Differences in type of stimulation coil, pulses/day, stimulation intensity, duration and cortical target may also influence outcomes.

Earlier rTMS-TS studies focused on prefrontal and premotor cortex as TS imaging studies have shown increased activities in

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these regions [9,10]. However, only one [6] of three studies [6–8] targeting these sites showed benefit. More recent open-label rTMS-TS studies were effective in tic reduction when targeting supplementary motor area (SMA) [2–5]. SMA plays a critical role in motor control [11–13] and is accessible to noninvasive brain stimulation. Several studies provide support for targeting SMA in TS. Functional MRI (fMRI) studies have found that SMA appears to be overactive in TS patients when performing motor tasks [14] and bilateral SMA are the most active regions immediately before tic execution [15]. Both fMRI and magnetoencephalography have shown increased functional connectivity between SMA and motor cortex in chronic tic patients [16,17]. A recent study of excitatory rTMS over SMA was shown to induce echophenomena in healthy adults [18]. Together these findings suggest SMA as a reasonable target for brain stimulation intervention in TS.

The objectives of this randomized, sham-controlled pilot study was to use fMRI to 1) provide individualized neuro-navigated rTMS stimulation of the SMA in TS/chronic tic disorder patients, and 2) to determine treatment-associated cortical changes. We hypothesized that repeated active rTMS stimulation of the SMA over 2 consecutive days would reduce tics compared to sham stimulation. We also hypothesized that this stimulation would alter the blood oxygenation level dependent (BOLD) signal change in SMA and primary motor cortex (M1) during a finger tapping task.

We chose to deliver a specific paradigm of rTMS called continuous theta burst stimulation (cTBS) [19]. The cTBS-induced neurophysiologic effect on M1 is similar to that of conventional inhibitory 1 Hz rTMS [20,21]. However, cTBS has benefits over 1 Hz rTMS in that the stimulation duration is much shorter and the stimulation intensity is lower, thus making this technique more feasible for pediatric patients. To further enhance the convenience and feasibility of this intervention, we compressed eight sessions of cTBS over 2 consecutive days as repeated cTBS sessions have been shown to safely produce significant neurophysiologic and clinical changes [22–25].

Methods and materials

Patient recruitment, diagnosis, clinical assessment

Patients (≥10 years old) with chronic tics were recruited from the Tourette Syndrome Clinic at the Cincinnati Children's Hospital Medical Center (CCHMC). Diagnoses were based on DSM-IV-TR criteria using direct physician interview. Inclusion criteria were 1) diagnosis of TS or chronic motor/vocal tic disorder, 2) Yale Global Tic Severity Scale (26) (YGTSS) score ≥20, 3) no medication changes within 10 days of receiving cTBS and throughout the remainder of the study and 4) no botulinum toxin injection within 12 weeks of starting and throughout the study. Patients with implanted metallic medical devices, pregnancy and epilepsy were excluded. Tic, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) symptom severities were assessed using validated scales – YGTSS, Gilles de la Tourette Syndrome Quality of Life Scale (GTS-QOL) [27], Premonitory Urge for Tics Scale (PUTS) [28], Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [29] and DuPaul ADHD Rating Scale [30]. Patients were also videotaped according to the Rush Video-Based Tic Rating Scale (RVTRS) [31]. These ratings were done by a blinded rater. Adult participants and parent(s) of pediatric patients gave written informed consent for the study, which was approved by the CCHMC Institutional Review Board. Children also gave written assent for the study. This study was registered with ClinicalTrials.gov (NCT01258790).

Experimental design

SWW, the only un-blinded investigator throughout the entire study, generated the randomization of active vs. sham stimulation (1:1) in blocks of four using Microsoft Excel. No other investigator had access to the randomization. SWW and DLG offered participation to all eligible patients. Agreed participants were sequentially assigned to a randomized condition after the consent/assent process during the first visit (Fig. 1). During the first visit, each participant underwent clinical assessment and fMRI by investigators blinded to treatment assignment. The TMS operators also demonstrated the TMS machines and obtained resting motor threshold (RMT). On visit 2, each patient underwent videotaping [31] and had repeat RMT measurements. Afterward, cTBS was delivered over the SMA using BrainSight2® software (Rogue Research Inc., Montreal, Canada) for individualized neuro-navigation based on fMRI data from visit 1. On the following day, each patient received repeated cTBS again over SMA. Immediately after the stimulation, the participant was videotaped [19] again and then underwent the second fMRI. Seven days later, the participants returned for videotaping [31] and clinical assessments.

Behavioral tasks

The finger-tapping motor task was used to isolate neural activity involved in motor planning and execution. This task had active and control conditions, both of which presented the participant with audio and visual stimuli. During both conditions, the participant heard a sequence of 1–4 tones (100 ms duration, 100 ms between tones, 100 Hz) and was presented with an image indicating to them as to whether they were on the active or control portion of the task. The active condition required the participants to tap their bilateral thumbs and index fingers together with the number of taps matching the number of tones heard. The control condition required the participants to simply listen to the tones. In total this task had 5 cycles of active and control conditions implemented as a block design with 4 active and 4 control conditions per cycle, one

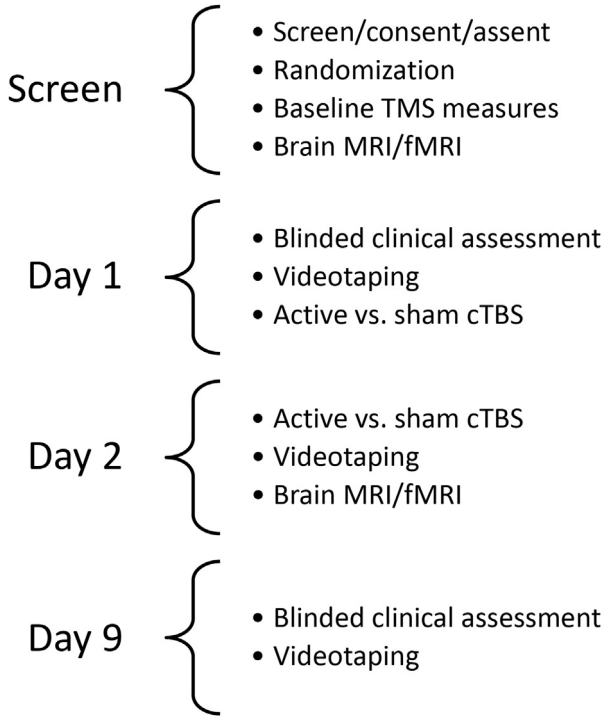

Figure 1. Study flow.