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A Double-Blind, Sham-Controlled Pilot Trial of Pre-Supplementary Motor Area (Pre-SMA) 1 Hz rTMS to Treat Essential Tremor

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Dear Editor:

Essential tremor (ET) is a potentially debilitating disorder for which there are limited treatment options and no available medical therapies except deep brain stimulation (DBS) for severe cases. The pre-supplemental motor area (pre-SMA) has a role in response inhibition in goal directed movement and is implicated in the pathophysiology of ET [1]. Dysfunction of the pre-SMA may be responsible for an unchecked oscillation in the cerebello-thalamo-cortical network, giving rise to the symptoms of ET. Transcranial magnetic stimulation (TMS) can noninvasively stimulate cortical brain structures using an electromagnetic coil to depolarize neurons [2]. TMS has been investigated in 5 prior ET studies [3] with mixed findings. 1 Hz rTMS of the pre-SMA region has been shown to improve inhibitory control over pre-potent ongoing responses [4], and we hypothesized that 1 Hz rTMS of the pre-SMA may tune abnormal oscillations in the cerebello-thalamo-cortical network, having an anti-tremoric effect.

10 TMS-naïve patients (6 women, mean 71.6 years (SD: 12.17, range: 41–82 years) who met the diagnostic criteria for ET [5] with visible upper limb tremor were enrolled from the Medical University of South Carolina (MUSC) outpatient neurology clinic. Patients signed a written informed consent approved by the MUSC Institutional Review Board (IRB) and a complete medical history was taken. Current medications were maintained and TMS contraindications or tremor inducing medications were exclusionary. Patients were enrolled, randomized (5 in each stimulation condition), and baseline assessments were made (videotaped administration of the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) [6] and ballistic wrist movement EMG recording). TRS ratings and evaluations were double-blind; raters and personnel were detached from the treatment condition. Upon completion of baseline recordings, patients started a course of 15 daily (Monday through Friday, weekends off) active or sham rTMS sessions administered by a technician aware of which condition the patient was receiving. Patients finishing the treatment phase completed a post-assessment in which baseline recordings were repeated. Lastly, patients presented to the MUSC Murray Center for Parkinson's Research for 4- 8- and 12-week follow-up visits in which a videotaped TRS was conducted. A timeline of the study is exemplified in Fig. 1a. This study was approved by the MUSC IRB and is registered on ClinicalTrials.gov (#).

rTMS was delivered using the Magventure Magpro X100 and cool B-65 A/P coil system (Magventure Inc, Denmark). Resting motor threshold (RMT) was determined weekly using the adaptive parameter estimation by sequential testing (PEST) [7] and visual inspection of digit or hand movement. rTMS was delivered to the pre-SMA along the sagittal midline (50% of the distance between EEG electrode positions Fz and FCz) [8] at the following parameters: 1 Hz, 1200 total pulses, 110% resting motor threshold (rMT), 20 minutes total. Active stimulation consisted of real magnetic stimulation delivered through the active side of the coil. Sham stimulation was administered using the Magventure B-65 placebo system in which the sham side of the coil was placed over the pre-SMA (no magnetism delivered) and

electricity was delivered to scalp stimulating electrodes in the same pulse sequence as active stimulation replicating stimulation sensation.

All 10 patients completed the treatment phase and 4-week follow up visit. Two subjects dropped out of the follow-up phase due to perceived lack of efficacy and desire to pursue other active therapies; their 8- and 12- week follow-up scores were determined using last observation carried forward (LOCF) method. Both active and sham groups had similar baseline TRS scores (active: 36, SD = 8.276; sham: 34, SD = 5.385). After 15 daily rTMS sessions, the active group showed a significant reduction in TRS score (26.11% reduction, mean TRS decrease 9.4, SD 7.36, p = 0.0038). The sham condition also showed a reduction in TRS score (18.82% reduction, mean TRS decrease 6.4, SD 4.615, P = 0.0497). Upon 4- and 8- week follow-up, only the active group maintained significant decreases compared to baseline (17.77% decrease, mean point decrease 3, SD 2.64 p = 0.0497). Between-group analysis demonstrated only a mathematical difference between stimulation conditions. Improvement in patients receiving active treatment was visually demonstrated in both handwriting and Archimedean spiral drawings section of the TRS (Fig. 1c).

A mathematical but non-significant change was observed in latency between first and second agonist bursts in the flexor carpi radialis during ballistic wrist movements of 30 degrees (active latency decrease 0.029s). 15- and 60-degree movements showed no change after treatment.

This is the first randomized controlled trial of low frequency rTMS of the pre-SMA for treating ET. Our results demonstrate that 15 daily sessions of low frequency (1 Hz) rTMS to the pre-SMA rTMS produces a significant (26.11%) reduction in TRS from baseline in patients with ET, whereas sham rTMS showed a smaller (18.82%) reduction. These gains persisted at 4- and 8-week follow-up in only the active condition. Using these data, we are able to calculate a dCohen magnitude of 0.49 (moderate effect). Given this effect size, double-blind, randomized controlled trial involving two treatment groups (active and sham) and an 80% power would need to recruit 134 total subjects (67 in each condition) in order to find between group significant results.

This preliminary trial with a small number of patients merits replication in a larger cohort for definitive conclusions. As with any rTMS treatment trial, our effects could possibly be potentiated by increasing the stimulation dose, using image-guided targeting, or exploring alternative inhibitory parameters such as continuous thetaburst stimulation (cTBS) [9,10], Inhibitory pre-SMA rTMS is a promising treatment for ET that requires further exploration, incorporating the newly determined effect size revealed in this study.

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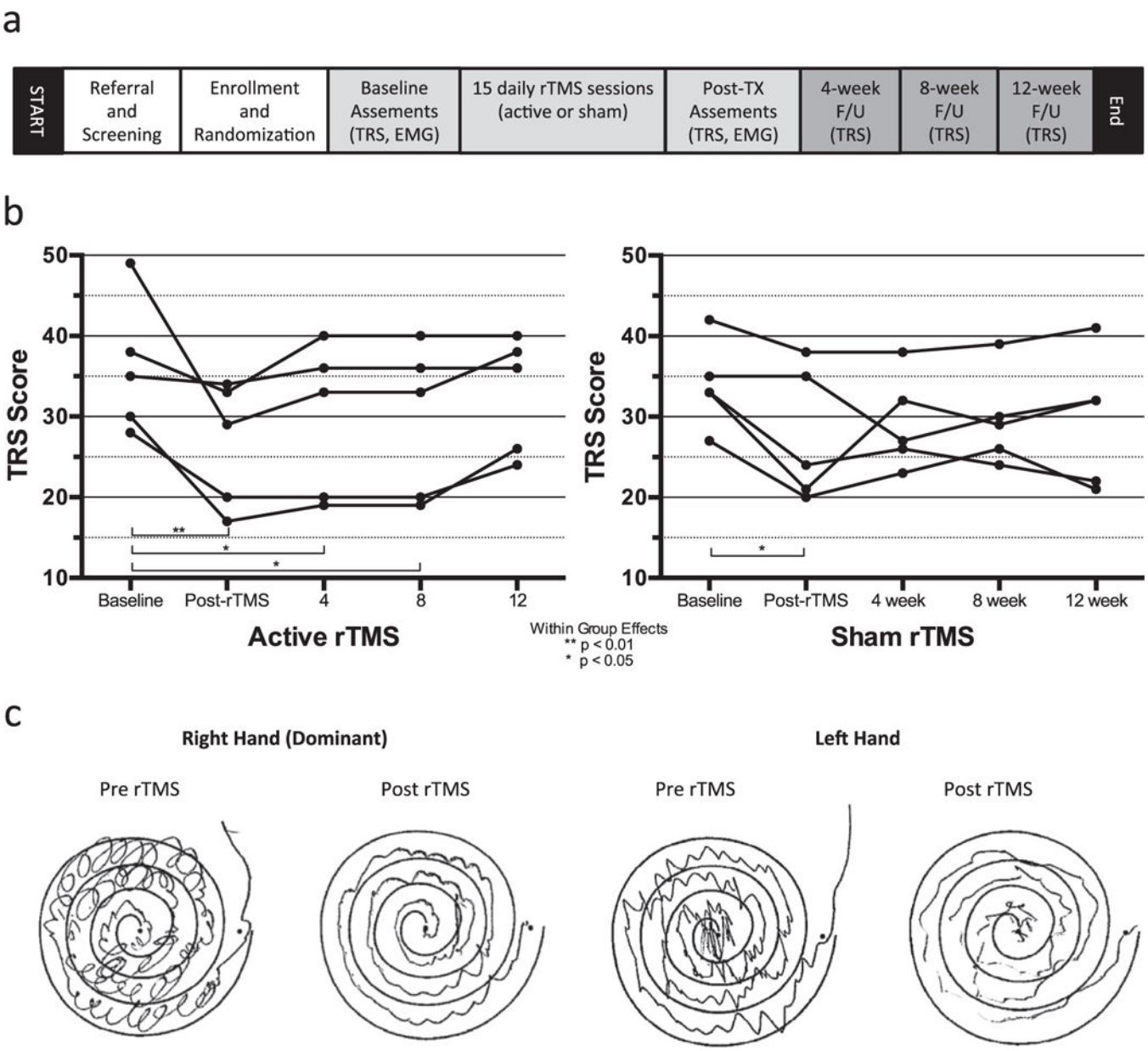

Figure 1.

(a) Timeline outlining course of the study. (b) Longitudinal tracking of individual patient TRS scores. (c) Pre- and post-rTMS Archimedean spirals for the best responder.