TMS for Improving Response Inhibition in Adolescents With OCD

NCT05104697

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Title of the Protocol:
TMS for improving Response Inhibition in Adolescents with OCD

Type of Investigation:
Double-blinded Randomized Crossover Trial

Objectives of the Investigation:
The study will examine whether inhibition of the pre-supplementary motor area (pSMA) using transcranial magnetic stimulation (TMS) normalizes activity in pSMA-connected circuits, improves response inhibition, and reduces compulsions in adolescents with OCD.

Participants:
The participants for this study will consist of 14 youth ages 13-18 years with OCD.

Duration of the Investigation:
Length of the study is one year. Duration of the study for individual participants will be 3-4 weeks.

Study Design:
We will use a within-subject, counterbalanced design comparing TMS vs Sham in a brief 2-visit protocol enrolling 14 youth (age 13-18) with OCD. At each visit, youth will complete the Stop Signal Task (SST) with concurrent electroencephalogram (EEG) pre- and post- TMS or Sham. TMS will be delivered over pSMA using continuous TBS (cTBS). After each visit, youth will rate symptoms using ecological momentary assessment (EMA).

Study Procedures:
Overall, study procedures include (a) pre-screening for initial eligibility determination; (b) clinical interview for final eligibility determination, (c) two study visits at which youth will receive TMS or Sham and complete EEG and SST procedures. Assessment procedures include structured diagnostic interviews, and safety screening for TMS. Interested participants will complete a brief phone screen and provide medical records for review before scheduling a clinical interview. Clinical Interview: Participants will complete informed consent (signature required from one parent/guardian), child assent, and assessment of inclusion/exclusion criteria (Mini Kid, CYBOCS, TMS screen; see Measures). Interviews will be administered by the RA, who is already employed at PARC and trained to a reliable standard on all measures. At each of visits 1 and 2, participants will complete a TMS safety screen and medication tracking form; they will then complete the SST with concurrent EEG pre- and post- TMS or Sham. The AEQ will be completed at the end of each visit. Between visits, youth will rate symptoms using EMA (see Measures). Visits 1 and 2 will occur at least one week apart to ensure that any acute TMS effects are no longer active by visit 2. Single session rTMS aftereffects on EEG suggests aftereffect durations <70 min[63].

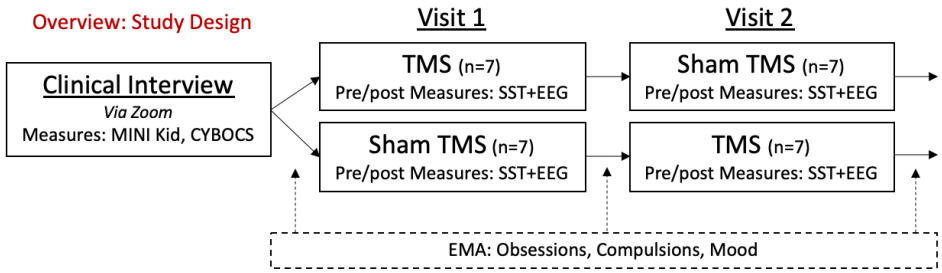
Inclusion Criteria:
- Age 13-18 years
- Presence of OCD, as indicated by score on the Children's Yale-Brown Obsessive-Compulsive Scale
- Patient and one parent speak English fluently (to ensure comprehension of study measures and instructions
- Right-handed
- If taking psychotropic medications, these have been stable for $\geq$ 6 weeks and are expected to remain stable for the approximately 3-week study protocol
- If currently in psychotherapy, symptom improvement has plateaued (no improvement in the past 6 weeks and symptoms expected to remain stable for the approximately 3-week study protocol)

Exclusion Criteria:

- Medical conditions contraindicated for TMS or EEG, including history of intracranial pathology, increased intracranial pressure, epilepsy or seizures, traumatic brain injury, brain tumor, stroke, implanted medical devices, possible pregnancy (female of childbearing age not using effective contraception), or any other serious medical condition (note that medical history will be reviewed by a study physician prior to TMS administration)
- Metal in the head, except mouth (e.g., cochlear implant, implanted brain stimulators, aneurysm clips)
- Active suicidality or psychosis
- Existing diagnosis of Autism Spectrum Disorder, mental retardation, or cognitive disability
- Substance abuse or dependence
- Taking a stimulant medication (and unwilling to forgo on study visit days)
- Taking medication with the potential to lower seizure threshold (e.g., neuroleptics, antipsychotics)
- Patient is a ward of the state

To increase external validity of findings, we will include participants taking psychotropic medications that have been stable for 6 weeks and expect to remain stable for the approximately 3-week study protocol (with the exception of those taking medications that reduce seizure threshold).

Study Design Flow Chart:



Study Assessment Measures:

1) Mini-Kid[64]; the Mini-Kid 7.0 is a brief, structured interview measuring psychiatric diagnoses in children according to DSM-V and ICD-10 criteria.

2) CY-BOCS[65], is the "gold standard" clinical interview for assessment of OCD symptoms.

3) Screening Questionnaire for TMS Candidates[66-67]; screens for TMS contraindications and will be administered in an interview format with both the child and parent present.

4) TMS Adverse Effects Questionnaire (AEQ[68]) is a 13-item questionnaire completed by patient (items 1-10) and clinician (items 11-13).

5) The SST is a well-validated computerized task measuring RI[69-70]. The SST is a visual choice reaction time task in which participants watch arrows (left or right) on the screen and respond by pressing the appropriate button. In a randomly assigned proportion of trials, an audible signal is heard after presentation of the arrow, and subjects are instructed to inhibit the motor response (button press). The inter-stimulus interval and stop-signal delay are varied according to individual performance so that each person can successfully inhibit responses to 50% of stop trials. SSRT (time required to inhibit a prepotent motor response) is calculated from these data. Successful stop trials (i.e., those in which a motor response is successfully inhibited) are most relevant for understanding functional neural correlates of RI, and will be of primary interest in EEG analyses (see below).

6). EMA will be used to obtain youth ratings on three items (modified from NIMH rating scales) assessing obsessions, compulsions, and mood on a 7-point scale (1 = not at all to 7 = very much). These items have shown differential change with frequent assessment post-TMS for adults with OCD[71] and have been used in EMA studies of OCD[72]. Youth will receive a text message prompt every two hours (between 9am and 9pm) over the two days following the clinical interview and each study visit (6 days total). The text prompt will include a redcap link for completing EMA items. Similar EMA items and procedures have been used successfully with adolescents of diverse backgrounds in a large number of studies to date[73].

7). HARM Form. At visits 1 and 2, we will administer the HARM form to assess for new or worsening suicidal or homicidal ideation (SI or HI). The Harm Form was developed for SI/HI monitoring by the Child and Adolescent Multimodal treatment Study (CAMS) team[105] and NIMH program staff and was also used in the POTS II and POTS Jr trials for youth with OCD[61-62]. The form is designed to ascertain the presence of any thoughts, wishes, or behaviors related to self-harm or harm to others since the last study contact. This brief measure consists of two broad initial probes—one asking about self-harm and the other about harm to others—and 5-8 contingent follow-up questions assessing acute risk status.

EEG procedures:

EEG Acquisition. EEG will be recorded continuously (band pass 0.1 - 100 Hz; sampling rate 10000 Hz) from the scalp using Brainvision system with the actiCAP slim 64 channel cap with a nose reference, along with additional electrodes to record the vertical and horizontal electrooculogram (EOG). All electrode impedances will be maintained below 10 kΩ.

EEG Data processing. EEG pre-processing: EEG recordings will be band-pass filtered between 1 and 55 Hz and visually inspected to remove segments with extreme motion artifacts. Noisy channels and dead channels will be removed, and the missing channels interpolated. To correct for eye-related artifacts (saccades and blinks), temporal independent component analysis will be performed[74-75]. The components that have a correlation higher than 0.8 with the EOG electrodes will be removed, and the remaining components will be added together to restore the EEG signal without the artifacts. The cleaned EEG will be segmented into epochs consisting of the time period during auditory stimulus presentation, along with a 100 ms baseline and a 500 ms offset period. Epochs with a voltage greater than ± 100 μV will be considered an artifact, and if the artifact cannot be corrected, will be excluded from the analysis. All EEG data preprocessing will be performed using the software package MNE-python[76]. Variable calculation. P3 is a well-established correlate of RI performance on the SST (including SSRT[55]) and of activation in inhibitory networks. We will calculate P3 amplitude on successful stop trials by averaging the epochs of successful stop trials time-locked to the stop signal from the midline electrode (Cz)[55].

Randomization:

The order in which participants receive TMS and Sham (visit 1 or 2) will be randomly assigned (blocking on medication status, biological sex, and baseline CYBOCS severity) and masked for all study staff except for the statistician.

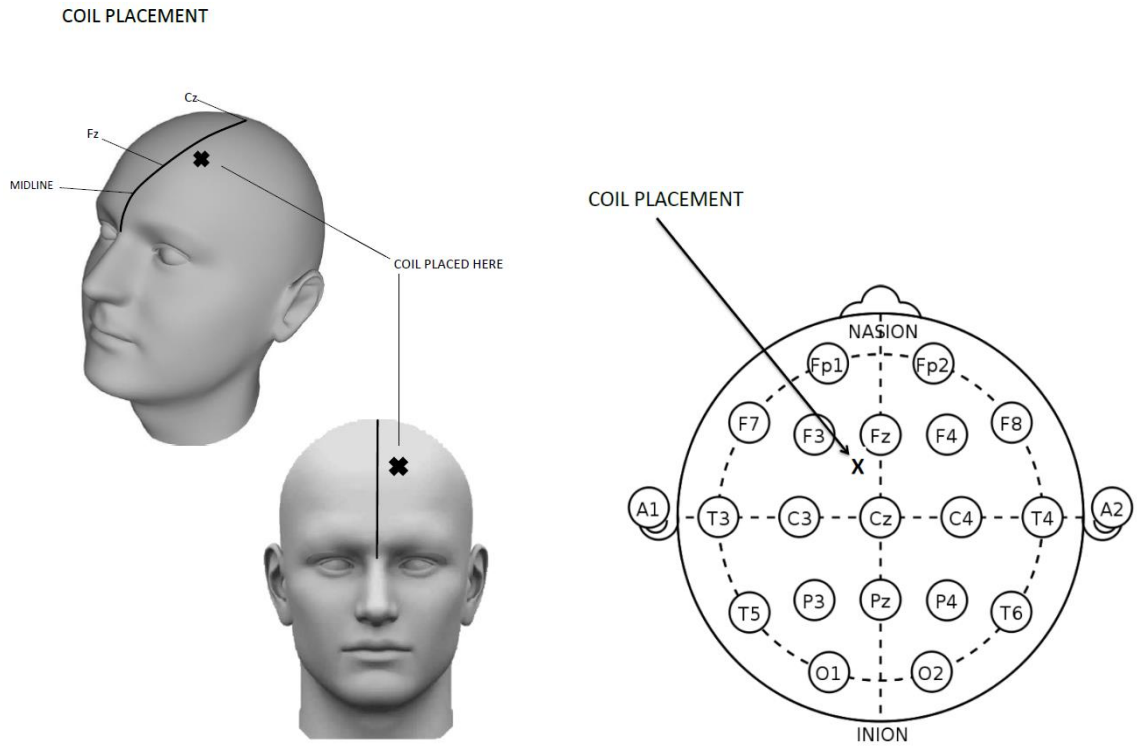
TMS Protocol:

During TMS, a pulsed magnetic field is produced by a small coil positioned over a targeted area on the scalp, inducing an electric current in the brain that temporarily modulates cortical activity. Repetitive TMS (rTMS) paradigms use trains of pulses to induce cortical effects that outlast the duration of stimulation.[63] The direction of the rTMS effect, either facilitation or suppression of cortical activity, depends on pulse frequency and sequence (i.e., intertrain interval). Research using neuroimaging and electrophysiological recordings has demonstrated that single low frequency (1Hz) and continuous bursting frequency (continuous theta burst stimulation; cTBS) induce inhibitory effects.[63,78-80] rTMS augmentation of cortical targets can impact local activity, connectivity, and network properties.[81] TBS and conventional rTMS have comparable effects on cortical excitability[82-83] and similar safety profiles in pediatric samples.[47,103] TBS has particular advantages for a pediatric population, specifically much shorter stimulation duration (i.e., 2-3 min for TBS vs. 20-30 min for rTMS) and lower stimulation intensity.[47]

TMS Device. We will use a Magstim SuperRapid2 Plus 1 TMS system with matching active and sham air-cooled coils (Magstim, Carmarthenshire, UK) (http://www.magstim.com, UK) to stimulate over pSMA target.

TMS Targeting. Targeting will be carried out using the 10-20 EEG system. Scalp vertex (Cz) will be defined based on the midpoint of the inion and the nasion on the sagittal midline. Prior research[77] has defined the SMA as 15% of

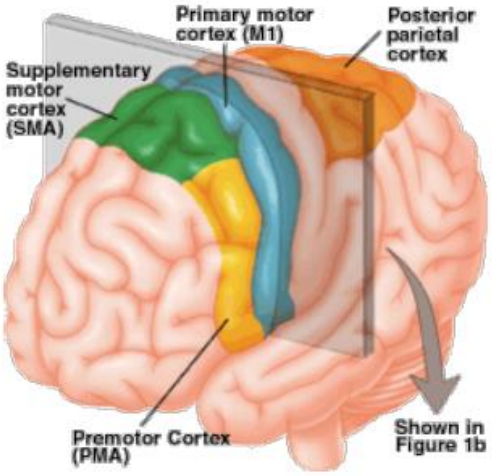
the distance between inion and nasion (I-N distance) anterior to Cz. Our research using neuronavigation to locate left pSMA indicated that average distance from Cz is 15.9% of the I-N distance anterior to Cz. Based on this information, we will target 16% of the I-N distance anterior to Cz (placement illustrated in the figures below, 1.5 cm from midline).

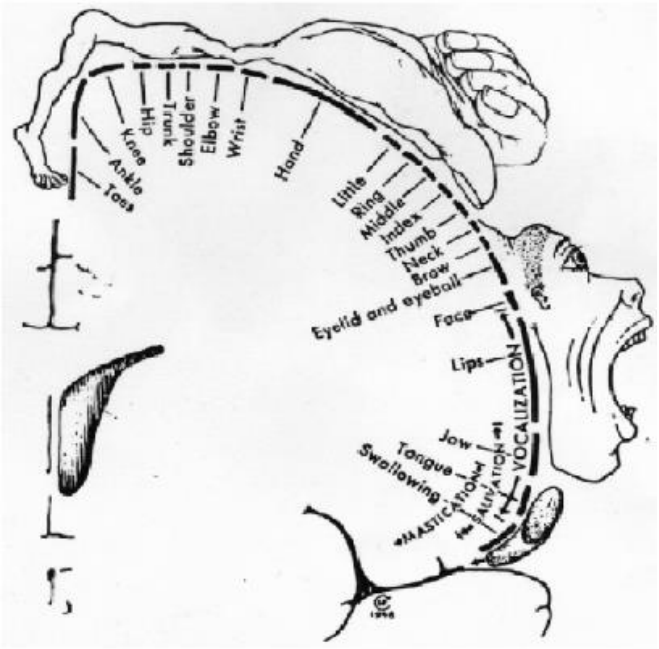


Category	Parameter
Coil type	
Shape	Figure 8
Size	70mm
Coil Placement	
Orientation	45°
Stimulation site	Left pSMA
Method for locating stimulation site	Scalp measurement based on 10-20 system
Stimulation parameters	
Pulse intensity	90% RMT
Pulse frequency	30 Hz
Train length	40 sec
Number of trains	1
Intertrain interval	0
Session parameters	
Pulses per session	3
Number of sessions	1

TMS Parameters. TMS will be delivered over pSMA using cTBS. Research using neuroimaging and electrophysiological recordings has demonstrated that single low frequency (1Hz) and cTBS typically induce inhibitory effects[63,78-80]. rTMS augmentation of cortical targets can impact local activity, connectivity, and network properties[81]. TBS and conventional rTMS have comparable effects on cortical excitability[82-83] and similar safety profiles in pediatric samples[47,84]. TBS has particular advantages for a pediatric population, specifically much shorter stimulation duration (i.e., 2-3 min for TBS vs. 20-30 min for rTMS) and lower stimulation intensity[47]. cTBS will consist of bursts of 3 pulses at 30 Hz repeated every 200ms (5 Hz burst frequency), single uninterrupted 40 sec train, 600 total pulses; 90% RMT. This sequence has been used in prior pediatric compulsivity samples[85]. 30 Hz is advantageous over conventional 50 Hz TBS in developmental samples as it can be delivered at higher stimulation intensity[86] and children have higher motor thresholds[87]. Single session aftereffects are approximately 60 min for cTBS[88-89].

Motor threshold (MT) determination. Resting MT will be defined as the minimum magnetic flux needed to elicit observed twitch of the thumb (resting target muscle: abductor pollicis brevis) in 5/10 trials using single-pulse TMS administered to the contralateral hand area of primary motor cortex (as described by Badran and colleagues[106]). The MT procedure will occur during the first visit and this MT will be used to calculate stimulation intensity for all TMS sessions. Patients will be in the same position (upright) during both motor threshold and stimulation procedures. The figure below demonstrates placement for eliciting twitch in resting target muscle (abductor pollicis brevis):





Sham procedures. Sham stimulation will use the Magstim sham air-cooled coil, which produces auditory signals identical to an active coil but contains a mu-metal shield that diverts the majority of the magnetic flux such that a minimal (<3%) magnetic field is delivered to the cortex. Forms assessing blinding adequacy will be given to participants, parents, and blinded staff who study visits.

Masking procedures will be implemented to control for expectancy effects related to TMS stimulation. Persons who will be masked to TMS status are: participants; parents (if applicable), study staff administering clinical assessments, SST, and EEG, study staff administering TMS, and all study investigators except for the study statistician responsible for randomization. Forms assessing masking adequacy will be given to participants, parents, and staff administering TMS. Study staff administering TMS will remain masked using the following procedures. The Sham and Active Coils are identical in appearance. The motor threshold coil which will be used for all procedures is different in appearance than the active and sham treatment coils. Each coil will each be labeled with a unique random number (e.g. 1639 vs 2740) but the technician will not know which is active and which is sham. The Neuromodulation Facility Manager will hold the masking log in a secure location. A masked TMS coil assignment log (included in CRF) will be used for the study with consecutively consented subjects assigned to consecutive ID#s that appear in the form. For each ID# there will be a coil number (e.g., 1639 or 2730) assigned in random order prior to start of the study. At the time of each treatment, the technician will confirm the participant's name and consult this form to select the correct coil to attach for the treatment session that day. The date of each session must be documented, along with the maximum intensity (relative to MT) applied in the session that day,etc.

Description of the Statistical Methods:

Statistical methods align with the Aims of the study, which are as follows:

Aim 1. Safety and Tolerability. TMS will be safe and tolerable, as indicated by a comparable rate of side effects associated with TMS vs. Sham (hypothesis 1) and no serious adverse events associated with TMS (hypothesis 2).

Aim 2. Neural Target Engagement: TMS-induced changes in the RI Network. Compared with sham, participants will demonstrate significant post-TMS neural changes during SST stop trials, as indicated by increase in frontocentral P3 amplitude

Aim 3. Behavioral Target Engagement: TMS-induced changes in RI behavior. Compared with sham, participants will demonstrate a significant post-TMS decrease in SSRT (Hypothesis 1) and EMA-rated compulsions (Hypothesis 2).

Data Analysis. We will test **Aim 1 (Safety and Tolerability)** using descriptive data as follows. Hypothesis 1. TMS will be safe and tolerable as shown by total AEQ ratings that are no more than 1 SD higher for TMS vs. Sham (hypothesis 1) and no serious adverse events associated with TMS reported on the AEQ (hypothesis 2). Remaining analyses will use Generalized Linear Mixed Models (GLMM), a variant of Generalized Linear Models (GLM; of which ANOVA, t-test, and regression are special cases) that permit outcome variables with distributions other than Gaussian and additionally permit modeling both fixed and random hierarchical (nested) effects. For each model, the distribution will be selected based on theory (e.g., Poisson for count) and model residuals. **Aim 2 (Neural Target Engagement).** We will examine the significance of TMS-induced neural changes during SST stop trials by testing an interaction between visit type (TMS vs. Sham) and timing of assessment (pre vs. post TMS/Sham) for the the outcome of frontocentral P3 (hypothesis 1). **Aim 3. Behavioral Target Engagement:** We will test an interaction between visit type (TMS vs. Sham) and timing of assessment (pre vs. post TMS/Sham) on RI efficiency as measured by the SSRT (hypothesis 1) and EMA-rated compulsions (hypothesis 2).

Sample size and power. We anticipate some minimal EEG/SST data loss and participant attrition, very conservatively resulting in a final sample size of N = 10 participants (each with four EEG/SST observations; pre- and post- TMS and Sham). Given this sample size and assuming .80 correlation among repeated measures, power calculations indicate that **Aim 2 and 3** analyses would reach 0.8 power with a medium effect size (Cohen's d = 0.51) and alpha = .05. Assuming .60 correlation among repeated measures, analyses would reach .8 power with a medium-large effect size (d = .70). Using a TMS protocol similar to that proposed in this application, Obseso (2017) found large effect sizes for cTBS of pSMA on SSRT in healthy adults (d = .95). Available data for proposed outcome variables suggest that repeated measures correlations will fall between .60 and .80, with SSRT showing correlations between .65-.73[101] and P3 showing correlations of .68-.71[102].

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