IRB Research Protocol

Title: STOP-TIC Study: **S**trengthening **T**ourette Treatment **OP**tions Using **T**MS to **I**mprove **C**BIT

NCT: 04795908

*Please note this is the original IRB document with the intended plan.

Background: Tourette Syndrome (TS) is characterized by multiple motor and at least one vocal tic persisting for at least one year."[1,2] Up to 20% of patients with TS have persistent tics during adulthood.[2,3] These tics can lead to impaired quality of life, social embarrassment, dysfunction in completing daily tasks, and complex tics can lead to pain or injuries.[4,5] Current treatments for TS have limitations: pharmacologic treatments are limited by their side effect profile and incomplete efficacy, and the evolving therapy of deep brain stimulation is an invasive surgery and not appropriate or feasible for most TS patients.[5-7] Comprehensive behavioral intervention for tics (CBIT) is an effective intervention for TS[8-10]; however, randomized controlled studies have shown less than 40% reduction of tic symptoms in adult patients with TS.[10-12] Therefore, there is a critical need to potentiate the benefits of CBIT, in order to open the door for innovative treatments that can improve the quality of life for patients with TS.

Transcranial magnetic stimulation (TMS) is a painless and non-invasive neuromodulation technique that uses a magnetic field to induce a cortically based electric field. TMS pulses delivered on a repetitive basis, known as repetitive TMS (rTMS), can modulate the brain networks involved in TS and potentially lead to clinical improvements. rTMS delivered at low-frequency (≤ 1 Hz) mimics long-term depression, leading to decreased cortical excitability. In contrast, high-frequency TMS (> 5 Hz) mimics long-term potentiation, leading to increased cortical excitability.[13] Further, rTMS delivered over multiple sessions has cumulative benefits that last beyond the stimulation period.[13,14] The pathophysiology of TS is still not fully understood. Singe-pulse and paired-pulse TMS studies in adults with TS have revealed normal resting motor threshold (RMT), shortened cortical silent period (CSP), and reduced short-interval intracortical inhibition (SICI), implicating cortical hyperexcitability as a potential mechanism for TS.[15-20] Functional MRI studies have shown that increased activity of the network connecting the cortex, striatum and the thalamus leads to more severe tics.[6,7,15,21-24] In addition, these imaging studies have shown that the supplementary motor area (SMA) is often hyperactive just prior to a tic occurrence.[6,24-26] The SMA is highly interconnected with the networks involved in the production of tics and is located superficially, allowing for penetrance by rTMS. The SMA is thus an ideal neuromodulation target for the TS population.[15]

There is emerging data from case reports, open-label studies, and small randomized controlled trials to that low-frequency rTMS targeted to the SMA can lead to tic reduction.[27-34] However, these studies are small, many involved only a single stimulation session, and the follow-up period was limited. Furthermore, these studies did not investigate whether rTMS in conjunction with CBIT could lead to synergistic benefits. rTMS is postulated to enhance motor and cognitive learning through the Hebbian mechanisms of neuroplasticity.[35-37] Thus, when rTMS is used in conjunction with behavioral and cognitive therapies, it may potentiate the synapses that are recruited to complete the intended tasks.[35,37] Therefore, the **primary goal** of this proposal will be to determine whether low-frequency rTMS delivered to the SMA has synergism with CBIT therapy in patients with TS. The central hypothesis of the proposal is that rTMS will potentiate the effects of CBIT, resulting in improved outcomes in patients with TS. In addition, given the known benefits of rTMS on depression and obsessive-compulsive disorder (OCD)[38,39], it is hypothesized that rTMS plus CBIT may not only lead to tic improvement, but also result in improvement in comorbid depression and OCD symptoms observed in patients with TS.

Since CBIT and rTMS both typically require multiple sessions over several weeks to be effective, these could present barriers to patient compliance. Delivering CBIT therapy via a virtual platform is just as effective via telehealth as it is in-person.[40,41] Accelerated rTMS protocols which condense the number of sessions into a consecutive day paradigm have been successfully and safely employed in other patient populations.[42-45] Therefore, a consecutive 4-day accelerated rTMS protocol followed by the recommended protocol for CBIT of 8 sessions in 10 weeks using a virtual platform will be implemented to mitigate these logistical challenges.

This will be an open-label study for which all subjects with receive active rTMS. Following active rTMS, all participants will undergo 10 weeks of tele-CBIT and whether rTMS will augment the effects of CBIT will be determined (**Aim 1**). The effects at baseline (T0), after rTMS (T1), and after CBIT therapy (T2)will be measured (Figure 1). In addition to the clinical outcomes, the physiological changes underlying the clinical effects will be investigated (**Aim 2**).

OBJECTIVES/SPECIFIC AIMS:

Specific Aim #1: Determine the clinical effects of rTMS combined with CBIT in TS.
The clinical effects of active rTMS + CBIT on tics and comorbid nonmotor symptoms will be determined. Tics will be examined with the standardized Yale Global Tic Severity Scale (YGTSS) and the modified Rush Videotape Tic Rating Scale (mRVTRS), and co-morbid symptoms with the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Adult ADHD Self-Reports Scale (ASRS). Quality of life will be assessed with the Gilles de la Tourette Syndrome – Quality of Life scale (GTS-QOL). I hypothesize that compared to baseline (T0), there will be greater reduction in tics (**Aim 1a**) and associated co-morbid symptoms and improvement of quality of life (**Aim 1b**) at T1 and T2 . I also hypothesize that the accelerated protocol will be safe and well tolerated in this patient population (**Aim 1c**).

Specific Aim #2: Determine the physiological effects of rTMS combined with CBIT in TS.
The physiological effects of active rTMS + CBIT will be determined using TMS and fMRI techniques. Cortical excitability will be determined with established TMS single and paired pulse paradigms including RMT, CSP, and SICI (**Aim 2a**), and resting state fMRI will be used to monitor the blood oxygen level dependent (BOLD) activity and connectivity of the SMA (**Aim 2b**). I hypothesize that the change in TMS measures will significantly improve and BOLD activity on fMRI will decrease over SMA at T1 and T2, compared to baseline and will correlate with the clinical improvements as outlined in Specific Aim #1.

RESEARCH PLAN AND METHODOLOGY: Patients with a diagnosis of Tourette's syndrome at our movement disorders center will be enrolled. Diagnosis of TS will be established in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

Inclusion Criteria: Any patient diagnosed with Tourette Syndrome > 18 years of age with moderate tic severity. Participants will be allowed to continue oral medications that they are taking for TS concurrently but will not be allowed to change their concurrent medication regimen throughout the duration of the study.
Exclusion Criteria: 1) Presence of metallic objects or neurostimulators in the brain, 2) pregnancy, 3) history of active seizures or epilepsy, 4) contraindications to receiving fMRI, such as claustrophobia 5) inability to participate in CBIT due to other underlying cognitive or medical condition

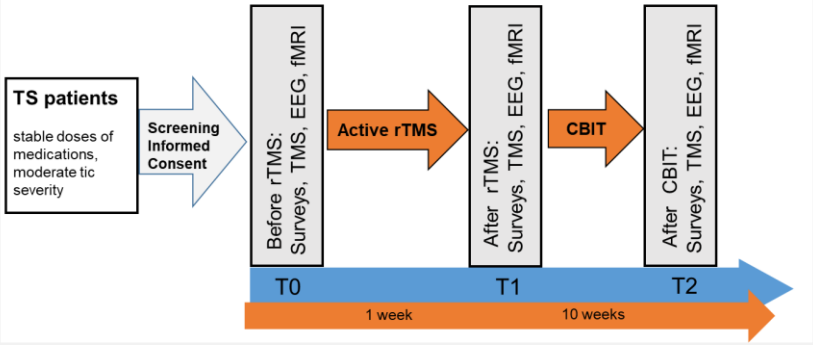

Figure 1. Study design and timeline. TS patients with moderate severity symptoms will undergo active rTMS followed by 10 weeks of tele-CBIT. Clinical, physiology measures, and imaging will be collected at three time points (baseline/T0, T1, T2).

Enrollment: Our target is to enroll 20 total patients in the study. In order to enroll 20, we will need to screen more than that number. We anticipate that we will need to screen 64 patients in order to find 24 that are eligible for enrollment. Of those 24, we anticipate that 4 will choose not to participate in the study.

IRB approved informed consent will be obtained. The study procedures will be explained, and subjects will have a detailed medical history and neurological examination. Patients will have primary and secondary outcome measures performed at four time points: Baseline (T0), following rTMS (T1), and following CBIT (T2)(Figure 1). The study protocol will take place over approximately 11-12 weeks. Details of specific parts of the protocol are included below.

Primary Outcome: Tic severity will be measured with YGTSS and mRVTRS. Videos of participants will be recorded at T0, T1, and T2,which will be scored by two independent blinded raters.
Secondary Outcomes: BDI, BAI, Y-BOCS, ASRS, and GTS-QOL; TMS, EEG, and fMRI outcomes.

rTMS protocol: rTMS will be delivered using a NeuroStar TMS therapy system (Neuronetics, Malvern, PA). The resting motor threshold (RMT) will be defined as the lowest stimulation intensity required to evoke a 50 μV potential in a target muscle (i.e. first dorsal interosseus muscle/FDI). A figure of eight coil will be used to deliver the stimulation. Patients will be seated in a comfortable reclined chair. The neurostimulation protocol will include 1-Hz rTMS over the bilateral SMA at 110% RMT. The SMA will be identified as 4 cm anterior to the vertex (Cz in standard 10-20 EEG setup). Each session will consist of 6 trains lasting 5 minutes each (300 pulses per train) with an intertrain interval of 1 minute for a total duration of 35 minutes (1800 pulses). Patients will receive 4 sessions each day on 4 consecutive days for a total of 16 sessions. Daily duration of this study protocol should last approximately 170 minutes including a 10 minute break in between each session (Figure 2). Constant coil position will be continuously monitored during the experiment. During rTMS, all participants will wear earplugs in order to protect the ears from the acoustic artefact associated with the discharge of the stimulation coil.

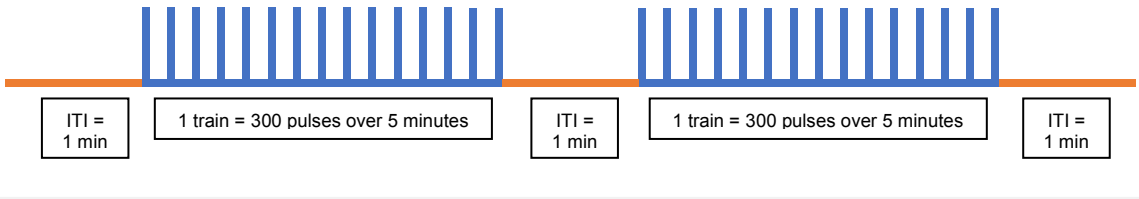

Figure 2. A schematic drawing representing a portion of an rTMS session. Each train consists of 300 pulses over 5 minutes (blue) and each intertrain interval (ITI) lasts for 1 minute without pulses (orange). Each session contains 6 trains alternating with an ITI. Patients will undergo 4 sessions per day, to be repeated for 4 consecutive days.

Single and paired-pulse TMS paradigms: The single and paired-pulse paradigms will be performed using the MagStim Bistim unit, which will be in the same room as the NeuroStar TMS machine. These will be followed per established protocols in the literature (Figure 3 A and C)[14,34] A single-pulse of TMS will be targeted over the motor cortex to generate a motor evoked potential (MEP), which can be captured on EMG. The rest of the EMG will be analyzed to assess the time between the TMS pulse and the MEP (also known as the latency) and the amount of time muscle activity remains silent following the MEP (also known as the cortical silent period). In a paired-pulse TMS paradigm, a subthreshold pulse will be provided followed by an interstimulus interval and then subsequent delivery of a suprathreshold pulse. When the interstimulus interval is short (1-4 msec), the ratio of MEP amplitudes produced by these two pulses is known as short interval intracortical inhibition (SICI).

fMRI protocol: Functional MRI will be used to record Blood Oxygen Level Dependent (BOLD) activity changes in patients at rest, using protocols similar to other studies in the literature in the TS population[34], as well as fMRI studies conducted by our group in other movement disorder populations.[46] The fMRI procedure should last approximately 1 hour. A 32-channel head coil will be used on a 3T MRI scanner. Subjects will wear earplugs during the sessions to minimize discomfort due to scanner noise. Anatomical images will be acquired in 170 contiguous axial slices at 1×1×1 mm resolution with a T1- weighted fast spoiled gradient-recalled sequence (repetition time (TR) = 6.8 ms; echo time (TE) = 3.3 ms; flip angle = 8º). Task-based functional MRI will be acquired in 46 axial slices at 3×3×3 mm resolution using a single-shot gradient echo-planar imaging pulse sequence (TR = 2500 ms; TE = 30 ms; flip angle = 80º). Each functional scan will include 176 TR volumes. Cushions will be placed in the head coil around the subject's head to minimize head-motion with strapping if needed. Repetition times (TRs), that include head motion exceeding 0.5 mm from TR to TR, will be excluded. Open source platform Analysis of Functional NeuroImages (AFNI: Version 16.0.19) will be used for the whole brain analysis. A combined 1.0-mm motion exclusion criterion in the x-, y-, and z-planes will be used. The following preprocessing steps will be followed. The first three functional MRI volumes will be removed to

account for scanner magnetization equilibrium. Following that slice-timing correction, rigid-body volume registration, co-registration of the functional MRI scan to the T1-weighted anatomical scan, non-linear spatial warping of the functional MRI scan to the MNIavg152 template will be performed. Signal-to-noise ratio will be improved by spatial smoothing using a full-width at half-maximum Gaussian kernel of 8mm.

CBIT protocol: All CBIT sessions will be conducted by an occupational therapist (Heather Simpson, OTD, OTR/L) who is a certified therapist in CBIT. Patients will have the option of having the first introductory CBIT sessions scheduled in-person since they will already be at the center for rTMS and outcome measures. For convenience, all other CBIT sessions will occur through a secure telemedicine platform. Each CBIT session will last approximately 1 hour. Following CBIT protocol, there will be 8-10 tele-CBIT sessions over 10 weeks, at the therapist's discretion. Each session will be individualized to each patient's needs depending on tic type and severity.

EEG protocol: High-Density EEG using 128 electrodes as the setup will be implemented. Each EEG session should last about 1 hour. Patients will be seated comfortably in a chair and a cap will be stretched across the scalp. This cap has 128 contacts where the electrodes will be connected using biosoluble glue. The electrodes will be placed appropriately by a clinician or technician trained to place the EEG electrodes. The patient's electrical activity will be recorded under two conditions: at rest and asking the patients to voluntarily suppress their tics (Figure 3B and D).

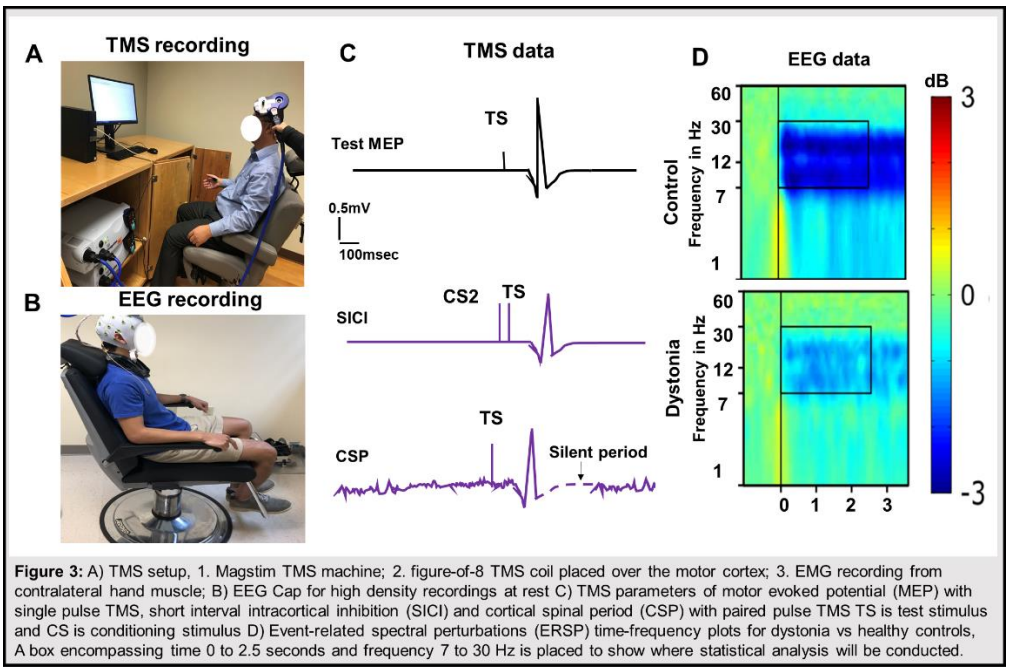

Figure 3: A) TMS setup, 1. Magstim TMS machine; 2. figure-of-8 TMS coil placed over the motor cortex; 3. EMG recording from contralateral hand muscle; B) EEG Cap for high density recordings at rest C) TMS parameters of motor evoked potential (MEP) with single pulse TMS, short interval intracortical inhibition (SICI) and cortical spinal period (CSP) with paired pulse TMS TS is test stimulus and CS is conditioning stimulus D) Event-related spectral perturbations (ERSP) time-frequency plots for dystonia vs healthy controls, A box encompassing time 0 to 2.5 seconds and frequency 7 to 30 Hz is placed to show where statistical analysis will be conducted.

Safety: Since the most important safety concern with rTMS is the possibility of seizure, participants with active seizure disorder or those at increased risk of seizure will be excluded. Low frequency protocols carry less risk of seizure as compared to high frequency protocols given that high frequency generates cortical excitability.[47] In spite of the theoretically increased risk of seizure in accelerated rTMS protocols, several accelerated high-frequency protocols have been safely performed in other patient populations and have been tolerated well by patients without evidence of increased adverse events.[42-45] A similar protocol to the one proposed in this study, using the same TMS system that I will be using, has been safely completed in the pediatric Tourette's population.[34] Patients will be screened prior to admission into the study, and those at risk for adverse reactions will be excluded. Those selected for participation will be monitored closely for adverse events. Other mild side effects that participants may experience secondary to TMS include transient eye pain, toothache, muscle twitch, facial pain, neck stiffness, and pain or discomfort at the application site and skin.

Clinical Assessments:

Yale Global Tic Severity Scale (YGTSS): This is a tool used to quantify the severity of tics through a semi-structured interview by assessing 5 components: number, frequency, intensity, complexity, and interference.

Modified Rush Videotape Tic Rating Scale (mRVTRS): This is a tool used by an objective examiner to quantify the severity of a patient's tics by rating the number of body areas affected, motor tic frequency, phonic tic frequency, motor tic severity, and phonic tic severity, each on a 0 through 4 score by watching a video of the patient.

Beck Depression Inventory (BDI): This is a 21-question survey evaluating depression in patients on a 0 to 3 scale.

Beck Anxiety Inventory (BAI): This is a 21-question survey evaluation anxiety in patients on a 0 to 3 scale.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS): This is a 10 question survey which rates components of obsessive thoughts or compulsive behavior and each question is rated on a 0 through 4 scale.

Adult ADHD Self-Report Scale (ASRS): This is an 18-question survey which asks patients to rate levels of attention, concentration, and organization as applied to daily tasks.

Gilles de la Tourette Syndrome – Quality of Life scale (GTS-QOL): This is a 27-question survey that asks patients to rate how their tics and abnormal movements affect their quality of life.

Patients will have primary and secondary outcome measures performed at four timepoints: Baseline (T0), following rTMS (T1), and following CBIT (T2).The study protocol will take place over approximately 11-12 weeks. All events related to the study procedure will take place within +/- 14 days of the expected timeline, with more details below (Figure 4). Patients will be compensated for their hotel stay during the 4 consecutive days of rTMS, and they will also receive compensation following completion of their time in the study in its entirety.

Figure 4. Timeline of study events and expected study activities at each timepoint.

Study Events (to occur +/- 14 days)	**Screening**	**Baseline (T0)**	**rTMS protocol (4 days)**	**Post-TMS (T1)**	**CBIT (10 weeks)**	**Post-CBIT (T2)**
Informed Consent						
Medical History						
Neurologic Exam						
Pregnancy Test (if woman of childbearing age)						
Demographics						
Active rTMS						
Tele-CBIT						
YGTSS						
mRVTRS						
BDI						
BAI						

Y-BOCS						
ASRS						
GTS-QOL						
MEP						
CSP						
SICI						
HD-EEG						
fMRI						
Study Compensation						

In order to participate in the study, patients will need to be present at the Fixel Neurologic Institute/University of Florida for 5 consecutive days at the beginning of the study, and will have to return in person for a single day after the 10 weeks of tele-CBIT.

Compensation:
Participants will receive $60 for taking part in the study (compensation for their participation)- this compensation will be prorated, so that patients will receive $20 in 3 equal installments, correlating with the T0, T1, and T2 outcome measure time periods.
Reimbursement:
In addition, participants who live a minimum of 50 miles from Gainesville will be offered a 4-night hotel stay of up to $125 per night in Gainesville so that they can complete the 5 consecutive days at the beginning of the study without having to travel back home each night- this will be paid at the time the patient and family are staying at the hotel. Participants (and family members/caregivers who accompany them) will additionally be compensated up to $150 ($75 for gas and $75 for food) during their visits to the Fixel Center/UF related to participation in this study. This will also be prorated so that they will receive $25 for gas and $25 for food in 3 equal installments at each of the outcome measure timepoints: T0, T1, and T2.

Data Safety Monitoring Plan: The research team monitors the patient safety and data collection of each study visit. The Data Safety and Monitoring Committee will meet once each year to review the recruitment, adverse events, data collection, and other aspects of the study. The Data Safety and Monitoring Committee will be notified of any adverse events that occur during the course of the study, within 2 business days of the specific adverse event. This will allow the DSMC to review any issues that arise in a timely manner. Breaches of confidentiality will also be monitored by the DSMC. If there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, the DSMC will be convened. If there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, the DSMC will be convened. Irene Malaty, M.D., Ashley Rawls MD, and Aparna Wagle Shukla MD will monitor the safety of the project yearly. Dr. Rawls will serve as an independent health professional on the Data Safety Monitoring Committee.

Location: The clinical portions of the study will be performed at the Fixel Neurological Institute; patients will have the clinical outcome measures collected in a clinic or research room.

The NeuroStar TMS machine is located in a separate TMS room within the Fixel Neurologic Institute. The MagStim Bistim machine is located in the same room.

Other devices necessary to complete the study include these portable devices which will reside in the TMS room during the study procedure:

EMG system: Bagnoli™ Desktop EMG system (Delsys, Inc., Boston, Massachusetts). It includes four surface electrodes to detect muscle movement
EEG system: ActiveTwo system (Biosemi, Amsterdam, Netherlands). It has a cap with electrodes in a preconfigured montage, using 128 Ag-AgCl electrodes.

The McKnight Brain Institute houses two 3 Tesla fMRI scanners for clinical research use, and is about a 10 minute drive from the Fixel Neurologic Institute.

Possible Discomforts and Risks: There are some possible discomforts and risks for participants taking part in this study, most of which are mild or transiently related to the study protocol and will abate afterwards.

TMS:

- Headaches – Headaches and neck aches can occur. They can be related to stabilizing the neck when measuring TMS. They are usually short lasting and respond easily to over the counter analgesics.
- Transient hearing threshold shift – There is a possibility of temporary mild hearing loss due to the noise of the TMS machine. The rate of this risk is unknown yet. Earplugs will be provided to the participant to reduce the potential for this risk.
- Seizure – A theoretical risk associated with brain stimulation. Since FDA clearance of TMS, the seizure risk is ≤0.1% per patient (less than 1 in 1000 patients). In the event that the participant has a seizure, the study staff will immediately stop the treatment session and make sure that the participant is safe during the seizure. The participant will be watched for a period of time after the seizure to make sure he or she is feeling well. Individuals with an active seizure disorder are excluded.
- Fainting – Not directly related to magnetic stimulation. It is thought to be related to anxiety and psycho-physical discomfort during the procedure. The laboratory is equipped, and staff is trained to respond to this risk if fainting occurs. However, the participant will be at very low risk (less than 1%) for fainting. Transfer to the emergency room might be needed if the participant fails to improve as expected.
- Effect of Magnetic Stimulation – Effect described on implanted devices (such as pacemakers, deep brain stimulation leads or cochlear implants). To avoid this potential complication, the participant will be excluded from the study if the participant has any metallic implants such as pacemakers, implants, metal rods or hearing aids.
- Childbearing Potential- There may be unknown risks to the fetus. Therefore, women of childbearing age will complete a pregnancy test for the TMS portion of the study at each visit. In order for the women of childbearing age to participate in this study, the participant should avoid becoming pregnant from their first day of most recent menses. A negative pregnancy test does not absolutely prove that a woman is not pregnant. If the female participant thinks that there is a possibility that she might be pregnant, the study team should be notified immediately. Nursing mothers are not eligible for participation in this project. The possibility exists that complications and undesirable side effects, which are unknown at this time, could occur.

EEG:

- A gel paste is used to attach the sensors during EEG which may mildly and briefly irritate the skin on the scalp or face. Hair products cannot be used on the day of testing (or should be washed out prior to testing), which may be inconvenient to the participant.

fMRI:

- Patients will need to lie flat for an extended period of time in a relatively enclosed space which may be uncomfortable for some patients. However, when safety guidelines are followed, an fMRI has minimal to no risk for the average patient. These rare risks include an allergic reaction to the IV gadolinium contrast used during the study and nephrogenic systemic fibrosis in patients with severe kidney disease. Patients with contraindications to fMRI, including documented gadolinium contrast allergy resulting in anaphylaxis,

severe kidney disease, or implanted medical devices incompatible with fMRI will be excluded from the study.

Possible Benefits: The participant may or may not benefit from taking part in the study. All participants will undergo CBIT, which has previously been studied and is one of the first-line treatments for TS given its favorable efficacy[11,48-49], so participants may benefit from participation in CBIT. Half the subjects will receive active rTMS which may augment the CBIT sessions, leading to even further reductions in tic severity and frequency. The information gathered from this study will benefit the neurology department and the larger research community as we continue to seek the most efficacious treatments for Tourette's Syndrome.

Regulatory Approval and Statistics: The study will be approved by the University of Florida Institutional Review Board, and all subjects will provide written informed consent. The study is highly feasible given the relatively large number of patients with Tourette's that are seen at UF. This is a pilot study so it has not been powered for statistical significance. We will use descriptive statistics and ANOVA to run analysis on the data that has been collected.

Confidentiality: Information collected about the patient will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the legal right to review these research records, and they will protect the secrecy (confidentiality) of these records as much as the law allows. These people include the researchers for this study, certain University of Florida officials, the hospital or clinic (if any) involved in this research, and the Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research). Otherwise the research records will not be released without participant permission unless required by law or a court order.

Researchers will take appropriate steps to protect any information they collect about participants. However, there is a slight risk that information about participants could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass them, or possibly even affect their insurability or employability.

If the results of this research are published or presented at scientific meetings, patient identity will not be disclosed.

Depression measure and suicide risk: If the Beck Depression Inventory reveals that the patient has feelings of harming themselves (Question 9 score 2 or above), we will refer them to mental health services available at Shands at the University of Florida.

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