Protocol Title	Transcranial Magnetic Stimulation to Augment Behavior Therapy for Tics
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Scientific Assessment	HRPP Scientific Assessment
IND/IDE # (if applicable)	G200176
IND/IDE Holder	Christine Conelea, PhD
Investigational Drug Services # (if applicable)	N/A
Version Number/ Date:	Version 1 – 07/14/2020 Version 2 – 12/15/2020 Version 3 – 4/8/2021 Version 4 – 7/20/2021 Version 5 – 10/26/2021 Version 6 – 2/24/2022

PROTOCOL COVER PAGE

ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact:*	**Required prior to IRB submissio**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:*	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submissio n.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/*	
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☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
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☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic	*Contact OBAO for submission instructions and guidance*	
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☐ **Yes** ☒ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff*	**Approval must be received prior to IRB approval.** **These groups do not have a separate applicatio n process but additional informati on from the study team may**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff*	**Does not affect IRB approval.**

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/15/2020	Added emergent unblinding procedures	no
2	4/08/2021	Updating screening process, randomization stratification procedures, monitoring entity, and online consent procedures.	Yes
3	7/20/2021	Adding recruitment strategies and adverse events monitoring in follow-up visits	No
4	10/26/2021	Added recruitment strategies and optional accommodations. Updated locations for study procedures	Yes
5	2/24/2022	Added recruitment strategies and transportation information	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

CBIT/Comprehensive Behavioral Intervention for Tics
SMA/ Supplementary Motor Area
rTMS/TMS/ repetitive Transcranial Magnetic Stimulation
ADHD/ Attention Deficit Hyperactivity Disorder
OC/OCD/ Obsessive Compulsive/Disorder
TST/ Tic Suppression Task
M1/ Primary Motor Cortex
CSTC/ Cortico-striatal-thalamo-cortical circuit
fMRI/MRI/ Functional/Magnetic Resonance Imaging
MEG/ Magnetoencephalography
DBS/ Deep Brain Stimulation
DLS/ Dorsolateral Striatal
cTBS/ continuous Theta Burst Stimulation
FT/ Free-to-tic
CMRR/ Center for Magnetic Resonance Research
MT/ Motor Threshold
FEM/ Finite Element Method
YGTSS/ Yale Global Tic Severity Scale
CNBD/ Center for Neurobehavioral Development
NDCT/ National Database for Clinical Trials
NIMH/ National Institute of Mental Health
GUID/ Global Unique Identifier
DUC/ Data Use Certification
FWA/ Federalwide Assurance
MINI/ Mini International Neuropsychiatric Interview
FIND/ Focus in NeuroDevelopment (Network)
NIBS/ Noninvasive Brain Stimulation Techniques
tDCS/ transcranial Direct Current Stimulation
ASD/ Autism Spectrum Disorders
ASAP/ Adjunctive Services and Attrition Prevention
RCTs/ Randomized Controlled Trial(s)
ITT/ Intent-to-treat
PMT/ Premature Terminators
MICE/ Multiple Imputation by Chained Equations
MSI/ Minnesota Supercomputing Institute
CAN Lab/ Converging Approaches to Neurodevelopment Lab
CTSI/ Clinical and Translational Science Institute
MAR/ Missing at Random
MNAR/ Missing Not At Random
RSFC/ Resting State fMRI Connectivity

ROI/ Region of Interest
GLM/ General Linear Model

LME/ Linear Mixed Effects
REDCap/ Research Electronic Data Capture
SAE/ Serious Adverse Events
PO/ Project Officer
NNL/ Noninvasive Neuromodulation Laboratory
MIDB/ Masonic Institute for the Developing Brain

1. Objectives

1.1. Purpose: The study will examine whether combining Comprehensive Behavioral Intervention for Tics (CBIT) with inhibition of the supplementary motor area (SMA) using transcranial magnetic stimulation (TMS) normalizes activity in the SMA-connected circuits, improves tic suppression ability, and enhances CBIT outcomes in young people with tic disorder. The study will also examine different TMS dosing strategies.

2. Background

2.1. Significance of Research Question/Purpose:

Chronic tics are a disabling neuropsychiatric symptom associated with multiple child-onset mental disorders. Chronic tics affect 1-3% of youth[1] and are associated with impaired functioning, emotional and behavioral problems, physical pain, diminished quality of life, peer victimization, and a fourfold increased risk of suicide compared to the general population.[2–4] Chronic tics are the primary symptom of Tourette Syndrome and Persistent Motor/Vocal Tic Disorders.[5] About 80% of those with tics have additional psychiatric disorders, most commonly Attention Deficit Hyperactivity Disorder (ADHD) and obsessive compulsive (OC) spectrum disorders.[1] High co-occurrence is attributed to shared dysfunction within cortico-striatal circuits.

CBIT is a manualized treatment program focused on tic management skills. Current American Academy of Neurology practice guidelines recommend CBIT as a first-line treatment relative to medications and other therapies.[6] Meta-analyses show comparable effect sizes for CBIT and medication.[7] Large randomized trials have demonstrated the superiority of CBIT over supportive therapy in child[8] and adult[9] patients. However, in these trials, only 52% of children and 38% of adults showed clinically meaningful tic improvement, meaning that 50-60% of patients do not benefit from CBIT.

CBIT success relies on an ability to suppress tics that many youth lack. The central aim of CBIT is to enhance voluntary tic suppression. Better tic suppression ability drives CBIT improvement[10] and predicts lower tic burden over the course of illness.[11] During the core CBIT procedure, competing response training, patients learn to inhibit tics by engaging in a competing motor action. However, research shows that many youth lack this fundamental tic suppression ability that CBIT aspires to enhance. Tic suppression ability has been assessed in our laboratory and others using the Tic Suppression Task (TST), which quantifies tics using direct observation methods.[12] Data show minimal changes in tic frequency when youth are instructed to suppress tics (e.g., reduction from a mean tic frequency of 4 tics per minute during “free to tic” baseline to 3 tics per minute during attempted suppression[13]). Under the most ideal suppression context--in which immediate reward is given for successful suppression--only 20% of youth

can suppress tics to near-zero levels, and another 20% show no detectable tic decrease or even tic worsening when attempting suppression.[12] Enhancing tic suppression ability is likely to enhance the efficacy of CBIT.

2.2. Preliminary Data: Our preliminary data show that tic suppression ability can be enhanced with inhibitory, noninvasive stimulation of supplementary motor area (SMA), an approach built upon established knowledge of tic neurocircuitry. Tics result from dysfunctional activity in cortico-striatal-thalamo-cortical circuits (CSTC).[14,15]

Tic generation involves the combined effects of excessive activity in sensorimotor pathways and reduced activity in cognitive control portions of CSTC circuits. SMA is a key CSTC cortical node, and SMA hyperactivity and hyperconnectivity is strongly implicated in tics. SMA links contextual cues to motor actions and plays a strong role in motor inhibition.[16] In healthy controls, excitatory stimulation of SMA with TMS produces tic-like movements and urges to move.[17] Similarly, direct stimulation of SMA with subdural electrodes produced urges to move in patients with epilepsy.[18] In those with tics, there is enhanced functional connectivity between SMA and successive nodes of the CSTC sensorimotor circuit.[14] SMA activation and functional connectivity abnormalities are significantly correlated with tic severity and complexity[19] and tic premonitory urge severity.[20] SMA activity is abnormally elevated prior to tic expression[14,21,22] and during periods of higher tic frequency.[22,23] Increased functional connectivity between SMA and primary motor cortex (M1; SMA-M1) has been shown in tic patients using fMRI[22] and MEG.[24] SMA shows strong resting state functional connectivity with striatal deep brain stimulation (DBS) sites most effective for treating tics[25] and with dorsolateral striatal (DLS) regions thought to normalize with CBIT treatment (i.e., putamen; SMA-DLS).[26] One small study (n = 8) examined neural correlates of CBIT using a visuospatial priming task and found normalization (reduced activation) in putamen following CBIT,[26] suggesting that CBIT engages striatal regions connected to SMA.

SMA's extensive connectivity with regions implicated in motor control and its role in tic pathology have made it a leading brain target candidate for noninvasive brain stimulation (NIBS) trials.[27] Repetitive TMS (rTMS) has been explored as a tic treatment in small trials,[28–31] some of which included children.[32–34] Early rTMS trials targeting premotor and motor cortex showed no effect.[30,31] In contrast, inhibitory stimulation of SMA using 1Hz rTMS has been associated with reduced tic severity in case reports[28] and open label trials.[32,34,35] Small randomized trials targeting SMA inhibition with 1Hz rTMS,[36] deep TMS with the HBDL coil,[29] and continuous theta burst

stimulation (cTBS) did not find group-level clinically meaningful change, although an extended dose (total of 6 weeks daily) did improve outcomes with 1Hz.[36] Importantly, in the only study measuring neural correlates of treatment, Wu et al.[33] detected significant decreases in activation of SMA and functionally connected CSTC nodes (i.e., bilateral M1) after only a 2 day course of cTBS, leading to continued interest in using TMS to alter tic-related neural pathology.

Our recent research suggests rTMS improves tic suppression ability more robustly than it reduces baseline tic frequencies. PI Conelea measured acute effects of 1 Hz vs. sham rTMS over SMA using the TST (K23MH103617; for detail see "Preliminary Data" below) and found that active 1Hz rTMS enhances tic suppression ability. Notably, reduction in tic frequency was more robust in conditions measuring tic suppression ability compared to a "free to tic" baseline. These data suggest that inhibitory stimulation of SMA with rTMS may benefit those with tics by enhancing their capacity to voluntarily inhibit tics.

2.3. Existing Literature: Taken together, the existing literature and our preliminary data suggest that augmenting CBIT with inhibitory stimulation of SMA using TMS may boost tic suppression ability, which in turn may increase the efficacy of CBIT. This synergistic approach aligns with converging evidence suggesting that combining brain stimulation with targeted therapy is a potentially powerful approach for treating neuropsychiatric disorders.[37]

3. Study Endpoints/Events/Outcomes

3.1. Primary Endpoint/Event/Outcome:

1) Neural target engagement: Within-subject change in resting state fMRI connectivity of SMA-mediated brain circuits.
2) Behavioral target engagement: Within subject change in tic suppression ability as measured by the Tic Suppression Task (TST).

3.2. Secondary Endpoint(s)/Event(s)/Outcome(s):

1) Two TMS procedures, both intended to inhibit activity in SMA, will be compared using data from our safety and feasibility measures.
2) Between group differences on secondary measures of clinical and neural function.

4. Study Intervention(s)/Investigational Agent(s)

4.1. Description: All participants will receive 10 daily sessions of CBIT, a well-established behavioral treatment that is considered by the American

Academy of Neurology to be the first-line intervention for tics.[6] Immediately prior to each CBIT session, participants will undergo TMS targeting the SMA. The specific type of TMS procedure will be randomly assigned between subjects and be either: 1 Hz repetitive TMS (rTMS), continuous theta burst stimulation (cTBS), or sham stimulation.

4.2. Drug/Device Handling:

TMS device. Stimulation will be delivered using a Magstim Super Rapid2 stimulator (Magstim Company Ltd, UK). The device will be used to deliver electromagnetic stimulation through a small coil positioned over a targeted area on the scalp. The manufacturer's indication for use is to stimulate peripheral nerves and the human cortex for diagnostic and research purposes.

We will use a Magstim air-cooled 70mm figure-eight coil for motor threshold determination and active TMS conditions. 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.

The device is installed and set-up at the University of Minnesota Non-Invasive Neuromodulation Laboratory (NINL). The device will only be able to be administered by trained personnel. The device is located in a locked, access controlled room.

Operation of the TMS device (MAGSTIM Super Rapid 2) will follow the procedures outlined in the attached "Operating Manual."

4.3. Biosafety: N/A

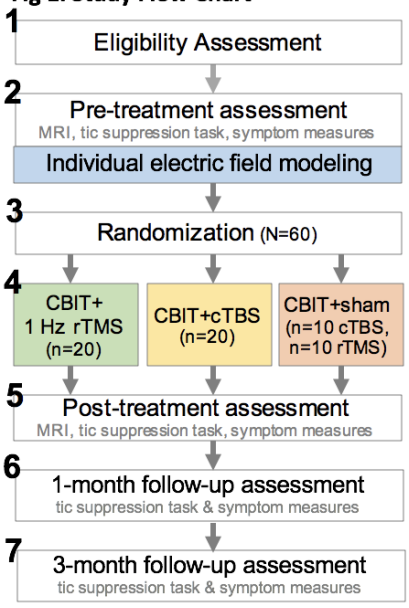
4.4. Stem Cells: N/A

4.5. Fetal Tissue: N/A

5. Procedures Involved

5.1. **Study Design**: The study is a double-blinded randomized control trial that will examine whether combining Comprehensive Behavioral Intervention for Tics (CBIT) with inhibition of the

Fig 1. Study Flow Chart



supplementary motor area (SMA) using transcranial magnetic stimulation (TMS) normalizes activity in the SMA-connected circuits, improves tic suppression ability, and enhances CBIT outcomes in young people with tic disorder. We will compare two rTMS procedures, 1 Hz rTMS and continuous theta burst stimulation (cTBS), against sham stimulation. Youth with chronic tics (n = 60) will complete 10 daily sessions of CBIT plus randomly assigned TMS procedure, with fMRI, behavioral, and clinical assessments before and after treatment and at 1 and 3 month follow-ups (figure 1).

5.2. **Study Procedures**: Overall, study procedures include (a) pre-screening for eligibility determination, (b) four assessment sessions (pre-treatment, post-treatment, 1-month and 3-month follow ups), and (c) ten daily sessions of CBIT+TMS. Consent and assent will be obtained prior to the start of the pre-treatment assessment visit (figure 1).

- **Eligibility Assessment** will occur prior to study enrollment. Parents/participants who contact study staff expressing interest in the study will be given a brief description of study procedures and asked to complete a phone or video chat (via Zoom) screen to determine preliminary eligibility. This screen is expected to take 25 minutes. Those potentially eligible will be asked to provide documentation of current medications. A signed release of information for medical record documents will be requested if necessary for eligibility determination.
    - **Optional detailed eligibility assessment:** In some cases, it is possible that phone screening outcome is unclear but could be clarified with an abbreviated version of the pre-treatment assessment visit focused on the specific eligibility question (e.g., whether tics meet minimum severity threshold). In these cases, we will conduct a focused eligibility assessment via Zoom. Consent/assent will occur at this visit. Measures will be selected from the list of approved measures for the pre-treatment assessment (Table 2, column 1). This assessment is expected to take no more than 1 hour. For participants deemed eligible, we will carry-forward data when possible and accordingly shorten the next assessment visit to reduce participant burden.
    - **Optional accommodations:** In order to ease participant burden, parent-report and self-report measures can be completed outside of the assessment or follow-up visit. All surveys must be completed within the 5 days following the visit date.

- **Study Assessment Measures:** Assessment procedures include a structured diagnostic interview, a clinician-administered rating scale for tic severity, parent-report and self-report measures for tic symptoms and other related emotional symptoms, and safety screening for MRI and TMS. Specific measures and the timing of administration are below in Table 1.
    - **Timing**: Consent/assent will be obtained at the first point of formal assessment (optional detailed eligibility assessment or pre-treatment assessment visit) (Step 2). Daily sessions of CBIT+TMS (Step 4) will begin within 10 calendar days of the pre-treatment assessment. Participants will complete 10 CBIT+TMS visits within 13 business days. The post-treatment visit will be completed within the 10 calendar days following the last CBIT+TMS visit. The 1-month assessment will be completed 4-6 weeks after the last CBIT+TMS visit, and the 3-month assessment will be completed 12-14 weeks after the last CBIT+TMS visit.

Table 1. Study measures		Steps in Fig 1					Time (min)
	Steps in flow chart (Figure 1)	1	2	4	5	6,7	
MEASURE	DETAILS						
Phone Screening	Eligibility, TMS safety screen[38,39]	x	x				20
Medical records	Last doctor visit, current medications, relevant/available documents; used for eligibility determination	x					
MRI safety screen	Eligibility	x	x		x		5
Demographics	Sample characteristics		x				10
IQ	Eligibility		x				15
MINI 7 KID[40] or adult[41]	Structured diagnostic interview		x				30

Yale Global Tic Severity Scale, YGTSS[42]	Gold-standard, clinician-administered tic severity scale. Includes symptom checklist of specific tic types.		x		x	x	30
Tic Suppression Task[12,43]	Direct observation measure of tic suppression ability		x	x	x	x	10
Parent/Adult Tic Questionnaire[44,45]	Adult-self or parent-report measure of tic symptoms and severity		x		x	x	5
Premonitory Urge for Tics Scale[46,47]	Self-report measure of intensity of urges to tic		x		x	x	5
Child/Adult Behavior Checklist[48,49]	Parent- or adult-self report measuring broad emotional and behavioral functioning		x		x	x	15
Sheehan Disability Scale[50]	Self- and parent measure of functional impairment		x		x	x	10
Tic Impact questions	Self- and parent-rated measures of how tics impact daily function		x		x	x	5
Behavior Rating Inventory of Executive Function[51]	Self- and parent-rated measure of impairment of executive function		x		x	x	15
Ask Suicide-Screening Questions (ASQ)	Clinician-administered screen of suicidality		x		x	x	5
TMS Adverse Effects Questionnaire[39]	Tracks side effects of TMS			x	x	x	5
Clinical Global Impressions (CGI)	Clinician, patient, parent-rated global measure of illness severity and improvement		x		x	x	2
Stimulation context tracking form	TMS operator completed form to track behavior and participant self-reported emotional state during rTMS stimulation			x			2
Blinding form (parent, staff, and child)	Assess belief about whether participant got active or placebo TMS				x	x	2
Concurrent Treatment Tracking Form	Record of all medications and dosages, psychotherapy		x	x	x	x	5
Client Satisfaction Quesitonnaire[52]	Assess patient satisfaction with the intervention				x		2
MRI	T1 and T2 structural, rs-fMRI, finger tapping task for TMS coil placement		x		x		60

- **MINI 7:** The Mini International Neuropsychiatric Interview (MINI) is a short, structured diagnostic interview, and is the most widely used neuropsychiatric diagnostic assessment tool in the world. The MINI is a tool used to conduct neuropsychiatric screening, diagnostic interviews, and outcome tracking for the most common adult and childhood DSM-5 and ICD-10 psychiatric

disorders. The MINI has been validated against the longer Structured Clinical Interview for DSM diagnoses (SCID-P) and against the longer Composite International Diagnostic Interview for ICD-10 (CIDI), and has been used in clinical care and research for more than 25 years. A digital version of the MINI 7 by Nview is available to researchers in the Department of Psychiatry & Behavioral Sciences and will be used. This program allows access to the MINI via web browser and stores data in HIPPA-safe Nview servers. Participant IDs will be indicated on MINI digital forms.

- **IQ assessment:** If subjects have not completed an IQ test within the previous 24 months from Step 2, they will complete a brief IQ test to determine eligibility for the study using either the Wechsler Abbreviated Scale of Intelligence, version 2 (WASI-2) or the Stanford-Binet Intelligence Scales, Fifth Edition (SB-5) (15 min).

- **Pregnancy testing:** Females who could potentially be pregnant will be tested for pregnancy and, if positive, will not be allowed to participate. If testing is refused, participation will not be allowed.

- **Tic Suppression Task (TST) procedures:** The TST will be our primary measure of behavioral target engagement. In this paradigm, a participant is seated alone in a room in front of a computer capturing a video recording of tic occurrences for later coding by independent raters. TST will consist of two 3-min conditions: 1) free-to-tic (FT): youth is instructed to stay seated and tic freely, a measure of naturally occurring tic frequency (tics per minute) ; 2) suppression: youth is instructed to suppress tics. Videos will be coded to establish tic frequencies using a computerized behavioral coding program.

- **Neuroimaging procedures. MRI and fMRI data acquisition:**A Siemens Prisma 3T scanner located at the Center for Magnetic Resonance Research (CMRR) will be used for image acquisition. To minimize motion artifact, we will immobilize the participant's head with foam wedges that fit snugly between the head and 32-channel receive only head coil. As needed, we will re-run scans or bring back participants for a repeat scan session. We will acquire the following data: 3D T1 ME-MPRAGE, 3D T2 SPACE, resting fMRI, spin Echo fMRI reverse phase encode scan pair, finger tapping task. The Finger Tapping Task will be used for functional localization of SMA. This task is used to isolate neural activity in

motor planning and execution areas, including SMA, and is a highly reliable, well-established fMRI task used for motor mapping[53] and for TMS targeting of motor cortex and SMA by our group and others.[33] A whole-brain activation map showing the contrast of rest vs. active tapping will be created for each person to determine the precise placement of the TMS coil.

- **Randomization:** Randomization will occur after pre-treatment assessments. Randomization will be stratified on baseline TST performance (tic suppressibility below or above 50%) and medication status (on vs. off).

- **Intervention Protocol: CBIT+TMS.** TMS will be delivered immediately prior to the start of CBIT sessions (see figure 2).

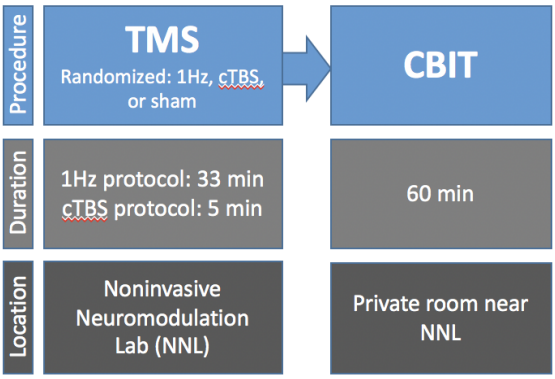


Figure 2. Flow of a single CBIT+TMS visit.

- **CBIT Protocol** will follow the published CBIT manual[54] tested in the large trials that established CBIT efficacy in children and adults.[8,9] Participants will receive 10 sessions of CBIT, 1 session per day across 10-13 business days. CBIT consists of the following components: 1) psychoeducation about tics; 2) functional interventions (behavioral strategies to decrease the impact of tic-exacerbating factors); 3) competing response training; and 4) social support to bolster skills use. Session 1 will include psychoeducation and creation of the tic hierarchy and sessions 2-10 will focus on competing response training. Competing response practice will be assigned for between-session homework. Monitoring CBIT integrity. CBIT sessions will be video recorded and a randomly selected 20% of sessions will be reviewed by the PI and rated using established CBIT compliance forms to ensure protocol adherence.

- **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.[55] 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.[55–59] TBS and conventional rTMS have comparable effects on cortical excitability[60,61] and similar safety profiles in pediatric samples.[62,63] 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.[63] Parameters for the current study are presented below.

- Motor threshold (MT) determination. Resting MT will be defined as the minimum magnetic flux needed to elicit a threshold EMG response (≥50 mV in peak-to-peak amplitude) in a resting target muscle (abductor pollicis brevis) in 5/10 trials using single-pulse TMS administered to the contralateral hand area of primary motor cortex. The MT procedure will occur during the first CBIT+TMS visit and this MT will be used to calculate stimulation intensity for all TMS sessions. Stimulation intensity may be adjusted to improve tolerability; all such adjustments will be reviewed by a study physician and documented.
- rTMS coil positioning: Individualized using fMRI and electric field modeling. TMS effects strongly depend on the spatial distribution of the induced electric field in the brain.[64] TMS targeting will be based on individual-level identification of the optimized coil location and orientation that induces the strongest electric field within SMA that show the highest parametric fMRI activation during the bilateral finger tapping task. This approach accounts for individual differences in physiology, which are prominent in developmental samples. We will create individual finite element method (FEM) models for each participant using the computer program SimNIBS (Danish Research Center for Magnetic Resonance, Copenhagen, Denmark and the Technical University of Denmark (Kgs Lyngby, Denmark) and participant anatomical MRIs, following procedures established by Co-I Dr. Opitz.[65–67] *Coil placement*. The coil placement and orientation will be based on the individual models and continually monitored using a stereotaxic neuronavigation system (BrainSight 2.3.5, Rogue Research, Montreal, Quebec, Canada) running on an Intel-based Macintosh computer (Apple, Inc, Cupertino, CA). This

system permits targeting of individual cortical locations using individual structural and functional MRI.

- TMS administration. TMS parameters are as follows:
    - Pulse frequency: 1 Hz, cTBS, or sham (randomized between subjects)
    - Pulse sequence:
        - 1 Hz: single train of 2000 pulses at 110% resting motor threshold (33 min duration)
        - cTBS: bursts of 3 pulses at 30 Hz repeated every 200ms (5 Hz burst frequency), single uninterrupted 40 sec train, 600 total pulses at 90% resting motor threshold (40 sec duration)
        - Sham: to enhance blinding, half of sham participants will be exposed to the 1 Hz sequence and half will be exposed to the cTBS sequence
        - Number of sessions: 10 day sessions, delivered daily on weekdays
        - Immediately after the stimulation ends, the participant will be transitioned to a private room for the CBIT session. The *TMS Adverse Effects Questionnaire*[39] will be completed by the participant and TMS operator at the end of each study visit.
    - rTMS sessions will be video recorded to later be coded for tic occurrences.

- **Blinding** procedures will be implemented to control for expectancy effects related to TMS stimulation. Persons who will be blind to TMS status are: participants; parents (if applicable); study staff administering clinical assessments, coding TST videos, delivering CBIT therapy, and collecting the MRI data; and all study investigators except Drs. Fiecas and Chen. Unblinded personnel will be Dr. Fiecas, the study statistician and person responsible for randomization scheme oversight; Dr. Chen, TMS operator supervisor; and the TMS operator. Staff who administer clinical rating scales and code TST videos will not be present for a given participant's CBIT+TMS visits to also ensure blinding to overall therapy progress. Staff will be trained and supervised on assessment scales by Dr. Jacob, who will audit YGTSS administrations for inter-rater reliability. Staff will be trained in TST coding by Dr. Conelea, who will code a set of video clips to monitor inter-rater reliability. For each of these measures (YGTSS

and TST), the supervisor will audit 100% of the first ⅓ of the initial visits, 50% of the second ⅓ of participants, and 20% of the third ⅓ of the participants for inter-rater reliability. Forms assessing blinding adequacy will be given to participants, parents, and blinded staff who conduct CBIT sessions and assessments visits at post-treatment.

- **Emergent Unblinding Procedure:** Unblinding of TMS status will occur in situations where staff deem this necessary for participant safety, to address a technical issue related to the TMS device, or another unforeseen situation in which TMS status is critical for study conduct. Unblinding will be limited to those individuals deemed most critical for addressing the inciting situation. Independent Evaluators (i.e., staff responsible for conducting pre-, post-, and follow-up assessments with participants) will not be intentionally unblinded to ensure that clinical functioning can be tracked by a staff member who is otherwise unfamiliar with the course of treatment.

- **Remote options and COVID-19 related protocol considerations**: The nature of the MRI and the TMS procedures requires that they be completed in-person. We will adhere to all COVID-19 related safety protocols and procedures for the facilities in which this equipment is located (NNL, CMRR), as well as our medical school approved laboratory Sunrise Plan. The consent/ assent and assessment procedures will be completed remotely via Zoom and REDCap if necessary due to COVID-19 social distancing precautions or optionally if preferred by participants (once social distancing is relaxed). Participants will complete CBIT sessions in a private research visit room in the Center for Neurobehavioral Development (CNBD) or the NNL. If needed for COVID-19 social distancing, the participant will interact with the CBIT therapist over Zoom to enable physical separation from the therapist. We will follow all University and facility protocols and recommendations for reducing COVID-19 risk in accordance with our CAN Lab approved Sunrise plans.

5.3. **Study Duration**: The total duration of the study for an individual participant will be up to 20 weeks (~4.5 months). The pre-and post treatment visits will take approximately 2.5-3.5 hours. Participants will have the option of splitting these into two separate visits within a week of each other, such that the MRI can be completed in a different visit than the rest of the assessment. The 1-month and 3-month follow-up assessments will take approximately 1.5 hours. CBIT+TMS visits will be approximately 1.5 hours. Enrollment of participants is

anticipated to take 3 years. Completion of all study procedures and data analyses are anticipated to take an additional 2 years after the final participant completes the study procedures.

5.4. Use of radiation*:* N/A

5.5. Use of Center for Magnetic Resonance Research: All MRI data will be acquired at the CMRR.

6. Data and Specimen Banking

6.1. Storage and Access:

- UMN: Questionnaire and video information will be stored on Box and will only be accessible to researchers. Research staff will access and analyze video records from AHC secured computers. MRI data will be stored and processed at CMRR. We will also store and process MRI and other data in the HIPPA compliant environment at MSI once that space is available.
- National Database for Clinical Trials (NDCT) related to Mental Illness: Per requirements of NIMH, the study funder, we will submit de-identified data to the NDCT.

6.2. Data:

- UMN: All psychometric and diagnostic data collected via questionnaire will be de-identified and stored in Box and the AHC server. Digital video data will not be altered and will be held in Box and secure AHC servers. MRI data will be stripped of file information containing PHI.
- NDCT: We will upload raw de-identified data twice yearly and all other de-identified data at the time of publication or the end of the grant. We will ensure proper information is gathered to generate a global unique identifier (GUID) for each participant. Data will be de-identified and include de-identified questionnaire information and quantitative output of video-based measures (i.e., tic frequency numbers from the TST, not the actual video).

6.3. Release/Sharing:

- Identifiable videographic data or MRI data: Releasing identifiable videographic and/or MRI data would be done through a rigorous approval system: Data resulting from videos and MRIs acquired during the proposed project may be shared. Qualified researchers can request access to shared data through the PI. Researchers can view summary-level data, or can request access to query and download subject-level data. Researchers who would like to access shared data must complete a Data Use Certification (DUC) form and submit it for review by the study team. There are three criteria researchers must meet to be eligible to request access: (1) the researcher must have a research-related need to access the data, (2)

the researcher must be associated with an NIH-recognized research institution, defined as an institution registered in the NIH electronic research administration system (eRA Commons), and (3) the researcher's institution must have an active Federalwide Assurance (FWA) and institutional IRB approval. Potential researchers must contract to destroy videographic and MRI data within 90 days of analysis, and provide a signed and witnessed Certificate of destruction. Researchers would be asked to cite the data source (University of Minnesota Psychiatry and applicable funding sources) in any published data resulting from the study.

7. Sharing of Results with Participants

7.1. Sharing Results: Participants will have the option to receive a written psychiatric diagnostic assessment report based only on clinically-validated questionnaires collected at the pre-assessment that can be used to inform care elsewhere. The report will be given directly to the parent or adult participant and will list any clinically significant diagnostic findings, such as positive diagnoses identified on the MINI. Minors will be informed of this. Participants will not be given individual feedback about other measures (i.e., TST, MRI) or clinical outcomes at post-treatment or follow-up; however, if participants/parents express interest in obtaining referrals for clinical care we will provide this assistance. Participants will be informed that overall study results will be posted on clinicaltrials.gov at the conclusion of the study.

7.2. Sharing Genetic Results: N/A

7.2.3 Future analysis of genotypes: N/A

8. Study Population

8.1. Inclusion Criteria:

- Age 12-21 years at time of enrollment.
- Current chronic motor and/or vocal tics, defined as tics for at least 1 year without a tic-free period of more than 3 consecutive months. Tics must not be due to a medical condition or the direct physiological effects of a substance.
- At least moderate tic severity, defined as a Yale Global Tic Severity Scale total score ≥14 (≥9 for those with motor or vocal tics only).

- Full scale IQ greater than 70.
- English fluency to ensure comprehension of study measures and instructions.
- Right-handed

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 intervention protocol (with the exception of those taking neuroleptic/antipsychotic medications). Those who previously received tic-specific therapy will be included if they meet the tic severity criterion. Youth receiving other forms of psychotherapy will be included provided these treatments are not focused on tics. All concurrent treatments will be monitored during the study period.

8.2. Exclusion Criteria:

- Medical conditions contraindicated or associated with altered TMS risk profile, including history of intracranial pathology, epilepsy or seizure disorders, traumatic brain injury, brain tumor, stroke, implanted medical devices or metallic objects in the head, current pregnancy or girls of childbearing age not using effective contraception, or any other medical condition deemed serious or contraindicated by a study physician (Dr. Jacob or Dr. Lim).
- Inability to undergo MRI.
- Left handedness.
- Active suicidality.
- Previous diagnosis of psychosis or cognitive disability.
- Substance abuse or dependence within the past year.
- Concurrent psychotherapy focused on tics.
- Neuroleptic/antipsychotic medications.
- Taking a medication that has not reached stability criterion (same medication and dose for 6 weeks with no planned changes over the intervention period)

8.3. Screening: A phonecall or secure video chat screening prior to study participation will be used to screen for inclusion/exclusion criteria. Exclusion criteria will be more thoroughly assessed during the pre-treatment assessment and by examining medical record documents. Medical history will be reviewed prior to rTMS administration using information gathered from participant/parent screening, which includes the Screening Questionnaire for rTMS Candidates questionnaire, and medical records obtained. If any potential exclusion criteria are identified where the

investigators judge more information is required for assessment, we will request relevant and available notes, lab studies, or talk to the participant's physician directly. Participants identified to meet exclusion criteria following the pre-treatment assessment will be discontinued from participation and will not complete subsequent study procedures or visits (i.e., MRI, CBIT+TMS visits).

9. Vulnerable Populations

9.1. Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Targeted Population
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	Included/Allowed to participate
Active members of the military (service members), DoD personnel (including civilian employees)	Included/Allowed to participate

Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to participate
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

9.2. Additional Safeguards:

- Children: The proposed study necessitates the inclusion of children because it focuses on a childhood-onset neurodevelopmental disorder. Tics begin in childhood and are most often studied and treated in children. The age period included in this study captures the period in which tics are typically at greatest severity, and it represents the typical age range used in existing studies on tic suppression and in TMS research focused on pediatric tic disorders. During adulthood, tics diminish for some impacted individuals, thereby making it less relevant to study tic treatments using adult-only samples. Currently, the first-line treatment for tics is CBIT, which all participants will receive. The risks associated with TMS are comparable to those posed by available medications for tics (https://n.neurology.org/content/92/19/896). Consent/assent procedures (described in 21 below) will ensure the parent and child

are fully informed of study procedures, risks, and benefits, and that the child is in agreement with participation and understands he/she is able to decline participation or withdraw without penalty. Procedures for minimizing risk are described below.

- Adult capacity to consent: Adult participants may be individuals with psychiatric or neurological conditions. We will assess capacity to consent by administering the MacCat-CR (MacArthur Competence Assessment Tool for Clinical Research); only those who pass the quiz (score at least 70%) will be deemed eligible to consent.
- Individual or group with a serious health condition for which there are no satisfactory standard treatments: It is possible that some participants will have tics that have not responded to currently available standard treatments. As this is a clinical trial aimed at testing a possible new option for individuals with tics, we will not exclude those who have serious tics and otherwise meet study eligibility criteria. Participants will be informed of the experimental nature of the TMS and the possibility that they may be randomly assigned to sham TMS.
- Other vulnerable categories: Our recruitment efforts will not specifically target individuals who are disenfranchised or disadvantaged or those in the military, but we will not exclude these individuals from participation.

10. Local Number of Participants

10.1. Local Number of Participants to be Consented: We plan to enroll 60 youth (ages 12-21 years) with chronic tics. Chronic tics have a known male preponderance, so we anticipate recruiting three times as many male than female participants.

11. Local Recruitment Methods

11.1. Recruitment Process:

- Flyers will be dispersed at the Department of Psychiatry and Behavioral Sciences, Center for NeuroBehavioral Development (CNBD), local mental health organizations, public physical and digital spaces (e.g. libraries, coffee shops, Minneapolis Reddit), community events, pediatric care facilities, for parents/adults to access and learn more about participation.

- Local physicians and allied professions likely to encounter youth with tics (e.g., psychologists, counselors, pediatricians, neurologists) will be sent an informational letter describing the study.
- Departmental websites will host information regarding the study and inclusion and exclusion criteria for participation. Potential participants will have the option of sharing contact information with us via a link to the attached "REDCap Recruitment Contact Survey." We will also post this information on the Research page of the Tourette Association of America. NAMI MN and other community groups we partner with will receive IRB approved language for online posting.
- The CAN Lab will utilize a social media Facebook page, Twitter account, TikTok account, Nextdoor account, and website to create an informative space about this research opportunity.
- The PI and study staff will conduct informational presentations about tic disorders for interested parties in the community (e.g., local mental health organizations, healthcare practice groups) in person or via webinars. For webinars, we will share information about the webinar and how to register publicly via CAN Lab social media and web pages. Registration will include the attached "Recruitment CAN Lab Permission to Contact" form. These presentations will be largely educational (e.g., what are tics, what the existing treatment guidelines are). Brief information about study activities, inclusion/exclusion criteria, and study team contact information will be shared at the end of these presentations.
- Potential participants may also find information about this study through the Focus In NeuroDevelopment (FIND) network.
- This study will be listed at ResearchMatch.org. ResearchMatch is an electronic volunteer recruitment registry that allows people from anywhere in the country to self-register and express an interest in being prospectively considered for participation in research studies. This registry provides information about those volunteers to researchers who are looking for people to participate in studies, while protecting the privacy of the volunteers.
- We plan on utilizing MyChart to reach out to potential participants within the Fairview system. Those who may be eligible to participate in the study will be sent a MyChart message that provides a brief description of the study and its procedures as well as the contact information for our team so the individual can reach out to us if interested. A copy of the MyChart message that we plan to send to potentially eligible participants are attached in ETHOS.
- We will distribute IRB approved digital flyers and a link to the attached "REDCap Recruitment Contact Survey" via targeted/paid advertising on

digital platforms including Facebook, Instagram, Peach Jar (a communication website between schools and parents).

- We will work with clinicians at M Health Fairview clinics who will invite us to speak with their patients potentially interested in the study who have not opted out of research participation. Clinicians will introduce the research and give a warm hand-off to a member of the study team either in-person or virtually. Virtual platforms will include AmWell, Doxy, and Zoom.

11.2. Identification of Potential Participants: Potential participants who self-identify in response to recruitment materials/activities and contact the research team will be screened for eligibility. Potential participants identified through the FIND Network and ResearchMatch will be contacted by a member of the study team.

11.3. Recruitment Materials: Recruitment materials include flyers, online posting, contact information surveys, and letters sent to health care providers who are likely to work with youth who have tics. Copies of these materials are attached in ETHOS. Finally, social media accounts under the "CAN Lab" will be maintained for this study. A coordinating website "CAN Lab" will also be used to delineate participation information. The website and Facebook page will also provide study team contact information and a link to the "REDCap Recruitment Contact Survey." The website and Facebook page will be compliant with HIPAA. No identifying information will be collected from these sources. Potential participants will be asked to directly contact the study team via phone or email or to complete the "REDCap Recruitment Contact Survey" for additional information and to learn more about study criteria. Registration for informational webinars will include the "Recruitment CAN Lab Permission to Contact" questions. The CAN Lab will use the University of Minnesota email: canlab@umn.edu for all email correspondence.

11.4. Payment:

- Participants will receive up to $350 for completing study tasks. Participants will receive $30 for pre-treatment assessments, $50 per MRI scan (for a total of 2 scans), $10 per day for 10 days for treatment (per session), $30 for post-treatment assessment, $40 for 1 month follow-up, and $50 for 3 month follow-up.
- Compensation will be provided at the end of each visit or in a bulk sum at the participant's request in the form of a GreenPhire ClinCard credit card.

12. Withdrawal of Participants

12.1. Withdrawal Circumstances: Anticipated circumstances under which participants will be withdrawn from the research without their consent include: 1) the participant does not/no longer meets inclusion/exclusion criteria; 2) study investigators decide that the participant has an emotional, physical, or behavioral reaction that poses a safety concern or interferes with data collection (e.g., poor compliance with instructions, too much anxiety to comfortably proceed with a task); 3) significantly deteriorating clinical course (e.g., emergence of acute suicidality); 4) significant adverse reaction to TMS, assessed using a TMS Symptom Rating Questionnaire daily; or 5) serious physical illness. Participants will be free to decide to withdraw at any time for any reason.

12.2. Withdrawal Procedures: Study withdrawals will be documented. When safe and feasible, participants who are withdrawn or who decide to terminate participation prematurely ("drop out") will be encouraged to return for a last assessment. This last assessment will consist of measures in the follow-up assessments (i.e., clinical measures only and not the MRI). We will make an attempt to provide participants with appropriate care referrals in the event of any withdrawals or drop-outs.

12.3. Termination Procedures: Individual participants will be considered to have completed study procedures after the 3-month follow-up assessment (or earlier as a result of drop-out or investigator-initiated withdrawal). The entire study will be complete after analysis of all identifiable data is complete. After termination of the project, only de-identified data will be used for analysis.

13. Risks to Participants

13.1. Foreseeable Risks:

- **General Potential Risk:** The participant and their parent(s), in the case of a child participant, may feel coerced to participate. Every effort will be made to emphasize that participation in the study is voluntary. To address the potential risk of feeling coerced, standard procedures for obtaining informed consent will be followed. Specifically, all participants will be reminded that their participation is voluntary and that refusing to participate or withdrawing from the project at any time will not result in any negative consequences for the participant or his/her family. In addition, adult participants and child participants and their parents will be fully informed of study procedures and potential risks and benefits at the start of the study. It is possible that some children may feel coerced into participation. In an effort to guard against this potential for coercion, children will be reminded that there will

be no negative consequences for declining to participate or to allow use of data (i.e., no one will be angry with the child). If any participants are also receiving clinical care at UMN, any discussions about participation will be conducted with a study staff member who is not part of their clinical team. This includes initial assessment of interest in the study, consent process, managing concerns, or discussing a potential study drop. We will also provide families with contact information for the UMN Human Research Protection Program (HRPP) and Dr. Conelea and welcome them to contact either or both to discuss any concerns they may have.We will also engage the participant by creating a pleasant, positive atmosphere, including breaks as necessary to minimize boredom, frustration, and fatigue.

- **CBIT:** CBIT has been tested in two large scale randomized trials, and there are no known risks associated with CBIT.[10,68]
- **Clinical assessment**: Assessment instruments and clinician-administered interviews are consistent with those typically used in research and clinical practices with this population. The youth and/or their parent(s) may experience emotional distress in being asked to provide information of a more sensitive nature. To address potential emotional distress experienced by participants from completing the assessments, questions will be presented in a supportive manner and participants will be assured that they may refuse to answer/participate in part or all of the questions/procedures. Participants will also be provided with multiple opportunities to take breaks. In addition, a clinical team consisting of licensed providers, Drs. Conelea, Jacob, and Lim, will be readily available. If participant **suicidality** or homicidality is reported during the course of the study, Dr. Conelea (or Drs. Jacob or Lim as back-up coverage) will follow standard clinical procedures to assess the severity and the suicidality and/or homicidality. As needed, participants/parents will be provided with appropriate referrals.
- **MRI:** There is some inherent risk with MRI, especially in regard to metal implants. There is risk of discomfort associated with loud noises and the small space available in the scanner. Participants will undergo a thorough screen to determine individual eligibility for the MRI. Prior to receiving an MRI, participants will undergo a screening process to determine MRI eligibility. Additionally, all participants will be asked to change into scrubs per CMRR policy in order to ensure they have no metal on their person at the time of the scan. All participants and their parents, in the case of children,

will be fully informed of the potential risk. Ear protection will be provided to the participants for protection from the loud knocking sounds produced by the MRI machine. Only trained and qualified MRI technicians will be performing the MRI tests. In addition, although unlikely, if the investigators notice an incidental finding on an MRI the parent or adult participant will be notified and given a recommendation to consult with their primary care physician. Scans will not be reviewed for any abnormalities. Subjects with self-reported anxiety associated with MRI procedures will not be included in the study.

- **TMS, general:** Noninvasive brain stimulation techniques (NIBS) have been used with thousands of children and adults. Three major review papers have specifically addressed the safety of TMS, rTMS, and transcranial direct current stimulation (tDCS) in pediatric populations.[76,139,140] Collectively, these papers indicate that NIBS has been used in healthy children and the following pediatric clinical conditions: tic disorders/Tourette Syndrome, stroke, attention deficit hyperactivity disorder (ADHD), major depressive disorder, autism spectrum disorders (ASD), multiple sclerosis, epilepsy and seizure disorders, malnourishment, Rett Syndrome, Cockayne's Syndrome, spasticity, schizophrenia/auditory hallucinations, language disorders, and dystonia. TMS is used as both a testing tool and a treatment. As a testing tool, the majority of children tolerate TMS well: in one study, 85% of the sample (n = 34 children) said they would do TMS again, and they ranked TMS as being more enjoyable than going on a long car ride, going to the dentist, or getting a shot at the doctor's.[141] No person experienced any change in their neurological examination, hearing, or any other tests that were performed, and all symptoms disappeared by the next day. Risks associated with rTMS are rare but should be recognized and prevented with appropriate precautions. Serious adverse risks include the induction of a seizure. Mild adverse effects include fainting, headache, dental pain, nausea, and other changes in memory, mood, and hearing. The overall occurrence of a mild adverse event is 5% in sham and real rTMS sessions combined.[142] rTMS delivery may also interfere with implanted devices. rTMS is not appropriate for persons with medical devices such as deep brain stimulators, pacemakers and medication pumps.

  Participants will undergo thorough screening to determine individual eligibility for TMS. Very extensive exclusion criteria are applied for participation in this study to ensure that enrolled

participants are not at any excess risk for medical adverse events. The only absolute *contraindication* to TMS is the presence of metal hardware in close contact with the discharging coil. Certain medications may increase the risk of seizure with TMS. Potential participants will be assessed for use of such medications. Individuals will be excluded from participation in the event they are currently taking any agents in this group. In addition, medical records reviewed by a study physician (Drs. Jacob or Lim) and completion of the Screening Questionnaire for TMS Candidates, developed by the Safety of TMS Consensus Group[69] will be administered and reviewed for TMS eligibility. An appropriately trained staff member will administer TMS and be present throughout TMS sessions to observe the participants. A standard questionnaire assessing side effects specific to TMS (TMS Adverse Effects Questionnaire[39]) will be completed at every TMS visit to identify and address any treatment-emergent adverse effects. The staff member delivering TMS will have updated first responder training, CPR training, and training in seizure management. The TMS administrator will immediately call 911 if serious adverse events occur.

- **TMS, seizure risk and management:** rTMS is FDA-approved as a noninvasive therapy for medication-refractory depression and obsessive compulsive disorder, where it is typically delivered at high frequency (10Hz). Its most significant potential risk is inadvertent seizure induction. Seizures have been associated with rTMS treatment in clinical research, particularly in the early trials (late 1980s - 1990s). Eight people (less than 0.8% of the total) had seizures associated with rTMS treatment in clinical trials conducted before safety guidelines were established. These guidelines, which specified safe ranges for rTMS parameters, have more recently been affirmed and further detailed in light of much more clinical and research experience with the method.[141] Seizures in animals and in adult humans have occurred only when the TMS magnet was used for impulses at sustained high-frequency (10Hz or greater), when the person had a pre-existing brain condition, or when the person was concurrently using a substance or medication. Based on the frequency of rTMS-related seizures reported in the literature, Rossi et al.[38] determined that rTMS is associated with a less than 1% risk of seizure induction for the general population and a 1.4% risk in patients with epilepsy. There are three documented

cases of TMS-induced seizure in youth, all using high-frequency rTMS. In a 2011 case report,[70] a 15 year old female with depression underwent high-frequency rTMS of 10Hz. The patient was taking a medication known to lower seizure threshold, sertraline 100mg. Follow-up of this patient over 4 months indicated no subsequent seizures or other complications. In a 2013 case report,[71] a 16 year old female with major depressive disorder underwent 10Hz rTMS. The patient was taking sertraline 150mg, olanzapine 75mg, and hydroxyzine 25mg. The seizure occurred on the 12th day of rTMS. The patient recovered completely without sequelae. Additionally, the examination revealed a high level of blood alcohol concentration (0.20%) at the time of the seizure, leading to a clinical diagnosis of TMS-related seizure complicated by alcohol use. A case study from a laboratory at UMN reported a seizure in an adolescent on the 8th day of rTMS treatment for depression using 18Hz stimulation with an H-1 coil.[72] No further seizures were reported through 6-month follow-up. Note that high-frequency, low-frequency, and theta burst rTMS have been used in youth and adults with tics, ASD, and OCD and no seizures have been reported in these populations. Theta burst stimulation has demonstrated similar risk/safety profiles as other rTMS protocols in pediatric populations.[63,73,74]

Management of potential seizures. As noted above, while seizure is very unlikely with the rTMS parameters and participant selection methods to be used, routine management of seizure will be carried out if needed. rTMS will be administered in a research area by trained personnel. TMS will be terminated immediately. The participant will be assisted in controlled reclining that prevents impact. Airway, breathing and circulation will be assessed. Unless tonic-clonic seizure activity occurs, the participant will be turned on one side to help clear the airway and avoid aspiration. Participants who convulse will be turned to one side as soon as movement ceases, and maintained in that position until recovery of awareness. Delayed recovery of normal consciousness beyond 30 seconds following a seizure will mandate a further medical and neurological evaluation. Note that initial measures for suspected seizures and syncope (see below) are identical.

- **TMS, uncomfortable sensations and pain:** The most commonly reported side effects of TMS are headache (lasting up to a few hours) and pain or discomfort at the treatment site on the scalp. A large-scale study on the safety of rTMS in depression found that headaches or scalp discomfort were typically mild or moderate. Headaches and neck pain are believed to be due to muscle tension. rTMS will be terminated if it produces discomfort which is not tolerated by participants. If a bothersome headache persists for several hours (which we think is unlikely), participants may choose to use an OTC pain reliever such as acetaminophen or ibuprofen for pain.
- **TMS, hearing**: While temporary hearing loss is a theoretical risk of TMS, available data indicate TMS has no demonstrable effect on hearing. All participants will wear ear protection (34 NRR earplugs) during TMS. In order to inform and protect participants, we will take the following precautions: 1) Inform participants of the risk of permanent hearing loss, if an earplug should loosen, become detached, or fall out; 2) Inform participants that they should immediately report to the research staff any loosening or detachment of an earplug during TMS; 3) Immediately stop TMS to replace earplugs if the participants reports or if a staff member observes that an earplug has loosened or has fallen out; 4) Ask the participant if they are experiencing any hearing problems following every session of TMS or if the parent has noticed any hearing problems since the last TMS session; 5) Prompt referral for auditory assessment of all individuals who complain of hearing loss, tinnitus, or aural fullness following completion of TMS.
- **TMS, syncope:** Vasodepressor syncope (fainting) is a common reaction to anxiety and psycho-physical discomfort. It is thought to occur more often than epileptic seizures during TMS, as with many other medical procedures. Participants will be monitored for feeling any signs or symptoms of a pending syncopal event (i.e., feeling dizzy or lightheaded). TMS will immediately be stopped, and the subject will be assisted. See *Management of potential seizures*, above).
- **Potential delay of non-experimental treatment.** All participants will receive CBIT, a well-established treatment that is considered by the American Academy of Neurology to be the first-line intervention for tics.[6] Because we exclude those with planned medication changes, participation in this study could cause a delay in effective pharmacological treatment with demonstrated efficacy.

- **Confidentiality.** Personal information collected during study procedures could result in social and/or psychological risk if released inappropriately. However, this is an extremely unlikely event considering all of the protective measures and precautions taken to keep data secure (see below). Researchers will be carefully trained about the importance of confidentiality and required to undergo HIPAA training.
- **Side Effects/Adverse Events**. Adverse effects will be monitored very closely throughout the study, through structured assessments and clinical interactions. At all visits involving TMS, the TMS operator will conduct a general inquiry regarding any health complaints, recent illness or injury, and need for medical consultation since the previous visit. Reported complaints will be coded on a standardized Adverse Events tracking form. Although unlikely, based on the nature of this study, the rater and study physician (Drs. Jacob and Lim) will rate whether the adverse event is related to the study or not. Dr. Conelea will then take relevant actions, which may include monitoring, adjunctive intervention within study protocol, or removal from the study.

13.2. Reproduction Risks: Currently, the effects of rTMS on hormonal cycles and the unborn fetus are unknown, therefore negative pregnancy test results and effective contraception will be required of childbearing age female participants.

13.3. Risks to Others: N/A

14. Potential Benefits to Participants

14.1. Potential Benefits: Several potential benefits exist. All participants will receive a psychiatric diagnostic evaluation without charge that can potentially be used by future or current health providers. All participants will receive CBIT, the first-line intervention recommended for tics by the American Academy of Neurology. Although not everyone who undergoes CBIT responds to the intervention, prior research shows that 50-60% of individuals experience an improvement in tic symptoms. Therefore it is likely that many participants will experience an improvement in tics from the CBIT alone (regardless of whether the experimental TMS augmentation has added benefits). Participants and their families may also appreciate the opportunity to talk about their thoughts and feelings with trained personnel. If our participants do not experience improvement in tic symptoms at the end of the study, we will ensure that they will be provided useful treatment and referral information. Participants and their families may also find benefit

in participating in research that may help others in the future. The information obtained through this study will also be of general benefit through adding to the body of knowledge concerning the treatment of chronic tics.

15. Statistical Considerations

15.1. Data Analysis Plan:

- **Treatment of missing data.**
  - **Strategies to minimize attrition**: Every effort will be made to reduce barriers participants and their families encounter in attending study visits. All study visits will be scheduled in advance, and staff will work with adult participants and parents to identify potential barriers to attending study visits in an effort to produce solutions.We will also implement an Adjunctive Services and Attrition Prevention (ASAP) plan to minimize participant attrition and effectively manage clinical crises, which may occur in RCTs involving a clinical sample. Thus, by using ASAP guidelines, more participants should be able to continue in their assigned intervention, which will enhance subsequent intent-to-treat (ITT) analyses. Each participant will be allowed 1 ASAP session during CBIT+rTMS phase and, in the R33 phase only, 1 ASAP session during the follow-up phase. Participants who exceed the maximum number of sessions within any treatment phase will be prematurely terminated as defined below.
  - **Premature Termination.** At any time, participants may deteriorate or develop clinical exigencies that lead study staff to recommend additional out-of-protocol treatments above and beyond that provided by ASAP guidelines (e.g., change in medications during the study). Such participants will be considered “premature terminators” (PMT) and classified as a protocol violation. In order to enhance the ITT analyses, "prematurely terminated" participants will continue to be treated within their assigned treatment arms insofar as possible, and assessments will continue according to protocol.
  - **Analysis** population will be an intent-to-treat population including all enrolled participants who completed at least 1 CBIT session.
  - **Treatment of Missing Data:** All participants will remain

in the study unless consent is withdrawn or there are concerns about patient safety. While there is little that can be done to address missing data when participants drop out during the training process itself, we can compare baseline characteristics of those who drop out at this time versus those who do not and adjust models based on significant predictors of dropout. For those who drop out during the follow-up period or miss some assessments during follow-up, we will use multiple imputation by chained equations (MICE) to allow for missing data without loss of those cases from the model under the assumption of Missing at Random (MAR). Sensitivity Analysis: If dropout status appears to be Missing Not At Random (MNAR), i.e., dropout is associated with an unobserved outcome, we will run sensitivity analyses using MICE to compare imputed and non-imputed models results to assess robustness of statistical inference**.**

- **Aim 1. Target engagement: Brain.** 1) **Primary** measure of neural target engagement will be decreased activation in SMA. Hypothesis 1: Either or both active TMS groups will demonstrate within-subject decrease (effect size $\eta 2=0.18$ in an ANOVA) in SMA activation post-treatment, as measured with an fMRI finger tapping task. While this is a large effect size in practice, we point out that Wu et al (2014) observed a much larger effect size of $\eta 2=0.41$ in the decrease in SMA activity comparing active vs sham cTBS. 2) **Secondary** measure of neural target engagement will be change in fMRI resting state functional connectivity of at least one SMA-mediated circuit (SMA-DLS, SMA-M1). Hypothesis 2: Either or both active TMS groups will demonstrate within-subject change (effect size $\eta 2=0.18$ in an ANOVA) in resting state fMRI connectivity (RSFC) of at least one SMA-mediated circuit (SMA-DLS, SMA-M1) post-treatment. A region of interest (ROI) analysis will be performed to determine the time*treatment group differences in SMA activation elicited by an fMRI motor task (finger tapping). The SMA ROI will be identified by placing a seed (sphere with 5mm radius) that matches the coordinate used for individual TMS coil placement. Activation parameters in the SMA will be identified in a first-level analysis, using a general linear model (GLM) to model each subject's SMA time course during the motor task. These activation parameters will be used in a subsequent linear mixed effects (LME) model. The predictors of the LME will include the baseline activation, group indicators for

the stimulation groups, and baseline x group interactions. Random effects will be used to model within-subject variation from the first-level analyses. Altogether, the LME will allow us to model how the within-subject change in activation from pre-treatment to post-treatment differs across active and sham conditions. *In addition*, we will also investigate the effects of each TMS regimen on the connectivity in the entire CSTC. To this end, we will extract the ROI-level time courses from each region in the CSTC, and we will use partial correlations to obtain an estimate of connectivity between each ROI pair within the CSTC while accounting for the data observed in the other ROIs. Given the collection of partial correlations for each study participant, we will use the SPU test, which uses the collection of partial correlations simultaneously, to assess for group differences across the sham and TMS regimens.[75]

- **Aim 2. Target engagement: Behavior.** Hypothesis: Either or both active TMS groups will show within-subject improvement (small effect size of at least Cohen's d = 0.3) in tic suppression ability as measured by the Tic Suppression Task (TST). TST "tic suppression ability" scores will serve as the primary outcome in an ANOVA model. An ANOVA will be used to establish if there exist differences in how the 1Hz, cTBS, and sham conditions affect change in tic suppression ability from pre- to post-treatment. Group indicators for these conditions will be the primary predictors for the model.

- **Aim 3. Assess dose-response relationship.** Changes in brain (Aim 1) and behavior (Aim 2) targets will be compared between active TMS groups (1Hz rTMS vs. cTBS) using ANOVA. In the case that both active TMS regimens are found superior to sham, we will compare the regimens on safety and feasibility. We will use 2-sample t-tests to compare the two regimens using data from our safety and feasibility measures and prioritize the regimen with significantly better ($p<.05$) outcomes.

15.2. Power Analysis: In Aim 1, hypothesis 1 our proposed sample size after accounting for expected attrition will give us 80% power to detect an effect size of at least $\eta^2=0.18$ for differences in SMA activation between active TMS and sham. For Aim 2, our proposed sample size will give us 80% power to detect an effect size of at least d = 0.90 for a within-subject improvement in tic suppression ability. Our preliminary data showed effect sizes of this magnitude.

15.3. Data Integrity:

- Dr. Conelea and Dr. Fiecas, the study biostatistician, will directly train the study staff in issues of maintaining data integrity. Dr. Fiecas will oversee data quality control measures and design a customized randomization procedure and data management system for this project. This study will utilize the secure, web-based Research Electronic Data Capture (REDCap) system for data input. Data checking procedures will be implemented to ensure data integrity. Data file archival and back-up will be performed on a regular basis

16. Health Information and Privacy Compliance

16.1. Select which of the following is applicable to your research:

☐ My research does not require access to individual health information.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

16.2. Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☒ Other. Describe: Medical record documents deemed necessary to determine inclusion criteria are met will be collected. Adult

participants or parents will provide these documents themselves or complete a release of information for us to request the documents directly from their provider.

16.3. Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed: Participants will self-identify for the study. We will not look at any medical records to identify potential participants.

16.4. Approximate number of records required for review: N/A

16.5. Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

Participants will self-identify and provide us with contact information and preferred method of communication (phone, text, email) during the initial phone screen. All outgoing emails will be encrypted using the University's encryption tool. Zoom video chat may be used for screening, assessment, and/or CBIT visits. We will use staff UMN Zoom accounts to host these calls. Video chats will be recorded on the AHC/HST devices listed below and uploaded immediately to Box.

16.6. Explain how the research team has legitimate access to patients/potential participants:

16.7. Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☐ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☐ Analyze ☒ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices: 20170192, 20171538, 20171356, 20150922, 20160281

☐ Store ☒ Analyze ☐ Share

☐ Other:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☒I will use a server not previously listed to collect/download research data: MRI data will be stored and processed at CMRR on the following IP addresses: naxos2: 160.94.164.170, lnpi14: 128.101.115.231, lnpi15: 128.101.115.161. We will also store and process MRI and other data in the HIPPA compliant environment at MSI once that space is available.

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☒I will use a mobile device such as an tablet or smartphone not previously listed: REDCap forms may be completed on a participant's personal device or device #20171356. REDCap surveys are completed via the internet, so no data will be stored on devices. Digital video cameras will be used to record study assessment, CBIT sessions, and the TST (20180803, 20120967, 20150922, 20171356, 20200509). Videos will be immediately uploaded to Box using an AHC-supported computer and deleted from the cameras.

Cameras will be stored in a locked cabinet in a locked room accessible only by study staff. If Zoom is used for these study tasks, we will instead record within Zoom and save videos directly to Box.

16.8. Consultants. Vendors. Third Parties: We will store and analyze data on Box. MINI-7 administration will use the Nview digital platform and the Dept. of Psychiatry account, which is HIPPA-safe and HIPCO-approved data entry program. We will utilize analysis software (such as SPSS, DataVyu) running on the AHC-IS supported devices listed above.

16.9. Links to identifiable data: Participant IDs will be used to label questionnaire, MRI, and video data. Consent and assent forms and any medical records obtained as part of eligibility determination will be stored in separate files from any data collected during the course of the study. We will have one file linking participant names and IDs that will be destroyed at the end of the study. The nature of the video analysis precludes de-identification of the videos.

16.10. Sharing of Data with Research Team Members: Data will be shared among research team members via AHC-IS server, REDCap, or Box.

16.11. Storage and Disposal of Paper Documents: Paper documents containing PHI collected in the course of this study will be retained by the study coordinator and kept in a locked cabinet in a locked research laboratory room in Diehl Hall suite 628. Paper documents will be digitized and stored on Box whenever possible. We will follow NIH and FDA guidelines for retention of records after the study concludes.

17. Confidentiality

17.1. Data Security: All data collected during the course of this research will be kept confidential and be used solely for research purposes described in our proposal. Data will be stored in accordance with HIPAA guidelines and accessed only by researchers and staff affiliated with this study. Data will only be accessible to research staff directly involved with the study who have completed HIPAA, CITI, CTSI, and Department required training. Access to the data will be completed through AHC secured devices and/or cloud-based HIPAA compliant programs (Box, REDCap). All video coding procedures will be conducted within data servers identified above. All data will be marked using confidential identification codes to minimize the risk of the breach in confidentiality. A key linking participants' identities and numerical subject codes will be stored in on Box. Questionnaire data will be

entered into REDCap and/or databases located on Box or the AHC supported server and be inaccessible to persons other than those on the study team. Consent forms will be stored in REDCap and backed up in a separate file location on Box from other study data. If any consent forms or study assessment measures are completed on paper (in the event of technical difficulties), forms will be scanned and stored in locked storage and digitized to Box. Only persons named on the IRB and involved in study coordination will have authorized access to consent forms and participant contact information. Videos of diagnostic interviews will only be reviewed by research staff for reliability purposes and erased at the conclusion of the study. During the CBIT+TMS visits, participants will be videotaped for the purposes of detecting tics during the TST and TMS and CBIT administration quality monitoring. These data will only be stored for research purposes. To the extent permitted by law, no participant information will be given to anyone without a signed release by the adult participant or child's parents. No identifying information will be used in written or oral presentations of results. No data or other information collected as part of this study will be placed in participants' medical, employment, or educational records.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

18.1. Data Integrity Monitoring:

- The PI will be responsible for data accuracy and quality assurance (e.g., data collection, entry, transmission, and analysis), trial management (e.g., enrollment, integrity of study procedures), and any interim analyses.
- The PI will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.
- The NIMH CTOB Clinical Research Education, Support, and Training Program (CREST) will provide ongoing monitoring of regulatory issues (e.g., SAE reporting, IRB actions, disclosures of conflict of interest). Frequency of monitoring visits will occur after IRB approval, as soon as possible after the first subject is enrolled, during the study data collection phase, and after the last participant has completed his/her participation in the study. This monitoring schedule may be revised based on considerations such as accrual rate, protocol deviations, magnitude of data corrections required, study stage (e.g. start-up or follow-up), or DSMB recommendation. Monitoring visits will be performed annually, at a minimum. The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

18.2. **Data Safety Monitoring:**

- **Data and Safety Monitoring Board:** A Data and Safety Monitoring Board (DSMB) will be included in this project. The draft DSMB charter is attached and will be reviewed and signed by DSMB members at the first meeting. The members of the DSMB include one board-certified psychiatrist with pediatric TMS expertise, one psychologist with CBIT expertise, and one biostatistician. Members will not be otherwise involved in this project and will not be collaborators on any other of the investigators' projects nor in their employ. Safety information will be collected with case report forms completed during study visits. They will meet prior to enrollment of the participant, after the first 10 participants are enrolled, and annually thereafter to 1) monitor the safety, quality and conduct of this study and 2) decide whether adequate participant safeguards are in place. The DSMB will review: 1) study progress, including assessments of data quality and participant recruitment, accrual and retention; 2) outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue, be changed, or terminated; 3) external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study; and 4) study procedures designed to protect the privacy of the research participants and the confidentiality of their research data. The study statistician will be responsible for generating a de-identified annual report of key events that will be reviewed as part of the safety monitoring of the protocol. The list of key events will specifically indicate: 1) seizures, 2) side effects to the study treatment, 2) hospitalization, and 3) premature drop-out from treatment. Any serious adverse events will be updated on an expedited basis. Members of the DSMB may request a conference call of the group at any time.

- **Reporting:** All investigators will report unexpected serious adverse events (SAEs) or unanticipated problems involving risks to subjects to the UMN IRB and to the assigned NIMH Project Officer (PO). Reports will be made to the DSMB (detailed above). If DSMB notes serious and unexpected adverse events, or unanticipated problems involving risks to subjects or others which are related to the study, the PI and UMN IRB will be notified. This will be done via a letter from the DSMB Chair/ Administrator to Dr. Conelea for distribution to the institutional official, sponsor, and UMN IRB. Dr. Conelea will also submit a yearly progress

report to the UMN IRB summarizing the data and safety monitoring activities and outlining 1) whether participants' safety, privacy and confidentiality has been consistently assured, 2) whether research instruments have been administered in a uniform manner and in a way that protects participants' privacy, 3) progress towards recruitment goals, quality of data collection (e.g., appropriate completion of forms), and participant retention/attrition rates, and 4) a review of new scientific literature pertinent to the safety of participants or the ethics of research participation. Dr. Conelea will report to the UMN IRB and the assigned NIMH PO within the following time frame: 1) IRB/ISM/DSMB suspensions or terminations (within 3 business days), 2) deaths related to study participation (within 5 business days), 3) unexpected SAEs (within 5 business days), 4) unanticipated problems involving risks to subjects or others (within 5 business days), 5) serious or continuing noncompliance (within 5 business days), 6) AEs deemed expected or unrelated to the study (with annual progress report), and 7) protocol deviations that do not affect the scientific soundness of the research plans or the rights, safety or welfare of the human subjects (with annual progress report).

19. Provisions to Protect the Privacy Interests of Participants

19.1. Protecting Privacy: All consent procedures, assessments, and study activities will be conducted in private rooms by trained personnel. Participants will be repeatedly reminded that sharing of information and completion of study tasks are voluntary. Assessment of participant comfort will occur on an ongoing basis; research staff will ask the youth how they are feeling and if they are comfortable with starting/continuing a study activity. Parents and children will be given the opportunity to separately discuss concerns or responses to questions with research staff. Since we are working with minors, we will inform participants and their parent(s) that we are required to report if the subject is a danger to themselves or others or if they report child abuse/neglect.

19.2. Access to Participants*:* It is necessary to access direct identifiers in order to maintain contact with the participant throughout the course of the study. Private information about the participant's health status is necessary to achieve study aims (e.g., psychiatric diagnoses, tic severity).

20. Compensation for Research-Related Injury

20.1. Compensation for Research-Related Injury: The following statement is included in the consent form: "In the event that this research activity results in an injury, treatment will be available, including first aid, emergency

treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study doctor know right away."

20.2. Contract Language: N/A

21. Consent Process

Consent Process (when consent will be obtained): Child assent and informed consent from the parent (to allow their child to participate in this study) or adult consent only (for participants aged 18 years or older) will be administered at the start of the pre-treatment assessment visit and will be required for participation in study procedures. Specifically, the consent and youth assent documents will be read through with all potential participants, and focus will be placed on potential risks and benefits associated with study participation, any alternatives to participating in the research, that opportunities to receive treatment will not depend upon research participation, clinical care will not be affected by study participation, and that participation is voluntary. In addition, the investigators will try to foster an open exchange of information, encouraging potential participants and their families to discuss study particulars and ask questions prior to research involvement; to receive a copy of the consent form to discuss with family and friends, if desired; and to continue asking any questions that might arise during participation. Parents/adult participants will be informed that all assessment information will be kept confidential with the following three exceptions explicitly stated: participant or parent (1) suicidality, (2) homicidality, and (3) abuse. Finally, details on written consent and child assent forms will be presented in simple language approved by UMN IRB. Among individuals who provide informed consent, only those who fully meet the study entry criteria after the pre-treatment assessment will be allowed to continue with the rest of the study. Participants who are active in the study when they turn 18 will be re-consented at the next visit/ session before additional study activities begin.

Potential participants will meet with the designated team member for assent/consent and potential enrollment. Consenting to research activities will take place in a private room at the Study Site or electronic consent may be conducted remotely, by phone or videocall. Participants over 18 years of age will need to meet via videocall or in-person for the administration of the MacCat-CR. These participants will not complete this procedure via phone call per institutional policies. During this visit, the qualified Site Study personnel authorized by the Site Principal Investigator and the potential participant and their parent/ legal guardian will discuss the nature of the trial, the purpose of the research, the trial procedures, the possible risks and benefits of participation, confidentiality and the voluntary nature of participation in the trial (emphasizing the participant's right to withdraw from the study at any time).

Following this discussion, potential participants and their parents/legal guardians will be offered the opportunity and encouraged to ask any study-related questions and enroll by providing written assent/consent on the IRB-approved form. For remote consent discussions, participants and/or their parent/legal guardian will navigate to the electronic consent/assent form shared through REDCap. The electronic consent/assent form has been designed so that the participant and their parent/legal guardian are unable to complete the consenting process without completing the consenting process with a member of the research team. Participants and/or their parent/legal guardian will first receive a "Read Only" version of the consent prior to the consent visit. Only after the research coordinator has completed the informed consent discussion and determined the parent/legal guardian and/or participant fully understand all procedures and are capable of informed consent will he/she sign the electronic consent form and deliver an "editable" version of the electronic consent form which the participants and/or their parent/legal guardian will be able to sign. For the electronic consent process to be considered complete, the consenting team member will access REDCap in real-time to confirm the parent/legal guardian and/or participant have signed the consent/assent form correctly.

Participants will be allowed as much time as needed, with Site Study personnel or in private, to review consenting documents before making the decision to participate. Potential participants may invite a friend or family member to be present during the visit, to further discuss their decision to enroll and/or contact (e.g., phone call) a friend or family member that is not physically present for discussion before deciding to enroll. At the potential participant's request, Site Study personnel may be asked to 'step-out' of the room or end/mute the call during remote discussions, to provide privacy for such discussions. In addition, potential participants will be provided the option to defer their decision to allow them to review the consent form and other study information forms at their convenience, and later reconnect with the Site Study team remotely or return to the Study Site to enroll (i.e., complete the informed consent procedures). No study activities will take place prior to completion of the consenting process.

21.1. Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.2. Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

21.3. Non-English Speaking Participants: N/A

21.4. Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

- Individuals under the age of 18 years will be considered to not have attained the legal age for consent to participate in research. Participants who are active in the study when they turn 18 will be re-consented at the soonest possible time before additional study activities are completed.
- Parental permission will be obtained from one parent, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
- Legal guardians will be allowed to provide permission if they provide documentation of their status as a legal guardian.
- Assent will be obtained from all of the children.
- The attached "Assent Form" will be used to document child assent prior to starting any study activities.

21.5. Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.6. Adults Unable to Consent: N/A

22. Setting

22.1. Research Sites:

- Participants will self-identify by calling a research assistant located in the CAN Lab, part of the Department of Psychiatry and Behavioral Sciences (University of Minnesota Twin Cities campus).
- Assessment visits will occur within the UMN Center for Neurobehavioral Development (CNBD) or remotely via Zoom. CBIT+TMS visits will occur at the CNBD and Noninvasive Neuromodulation Laboratory (NNL). MRIs will be conducted at the Center for Magnetic Resonance Research (CMRR).
- If transportation acts as a barrier to participation, we will provide assistance with Uber, Lyft, or taxi. Participants or a legal guardian will be required to provide additional consent for staff to arrange transportation for research participants.

22.2. International Research: N/A

23. Multi-Site Research

N/A

24. Coordinating Center Research

N/A

25. Resources Available

25.1. Resources Available:

- *Recruitment resources:* Dr. Conelea is a psychologist on the faculty of the Child and Adolescent Division of the Department of Psychiatry and Behavioral Sciences and will have access to referral sources and healthcare providers in the community who treat young people with tic disorders. The research team has access to the FIND Network to recruit from over 500 potential families with and without children with neurodevelopmental diagnoses. Additional recruitment efforts will be posted through the departmental and laboratory websites and social media. It is expedited that the research team will be able to recruit 60 participants through the delineated recruitment plan.
- *Facilities*: Private space for conducting participant visits is available at the CNBD. MRI acquisition will be available through the CMRR. We will have access to the TMS equipment at the Noninvasive Neuromodulation Laboratory.
- *Training:* Research staff will be directly trained in study procedures by Dr. Conelea, and she will continually assess their protocol knowledge and skill performance on an on-going basis. Additional supervision to research staff as needed will be provided by co-investigators with the relevant expertise. Dr. Conelea is supported by a Project Director, Dr. Sunday Francis, who will also support supervision and training of clinical research coordinators. All staff with access to research participants will have completed HIPAA and CITI training, and the University of Minnesota IRB's Assessing Capacity to Consent training (e.g., children). These standards will be upheld throughout the study period.
- *Medical or psychological resources for participants in event of an anticipated or unanticipated consequence of research:* The study investigator team includes a licensed psychologist (Dr. Conelea), psychiatrists (Dr. Lim and Dr. Jacob), and a pediatrician (Dr. Jacob). All are on the faculty in the Department of Psychiatry and Behavioral Sciences. As such, they will have access to referral sources within and outside of the department.
- *Time devoted to the research*: The PI, Co-Investigators, Project Director, and study staff will dedicate time to this project in accordance with funding provided via an NIMH grant. The research team will hold regular meetings to discuss study procedures and progress.

26. References

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