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Targeted Interventions in Tourette's using Advanced Neuroimaging and Stimulation (TITANS): study protocol for a double-blind, randomised controlled trial of transcranial magnetic stimulation (TMS) to the supplementary motor area in children with Tourette's syndrome

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ABSTRACT

Introduction Tourette's syndrome (TS) affects approximately 1% of children. This study will determine the efficacy and safety of paired comprehensive behavioural intervention for tics (CBIT) plus repetitive transcranial magnetic stimulation (rTMS) treatment in children with Tourette's syndrome. We hypothesise that CBIT and active rTMS to the supplementary motor area (SMA) will (1) decrease tic severity, and (2) be associated with changes indicative of enhanced neuroplasticity (eg, changes in in vivo metabolite concentrations and TMS neurophysiology measures).

Methods and analysis This study will recruit 50 youth with TS, aged 6–18 for a phase II, double-blind, block randomised, sham-controlled trial comparing active rTMS plus CBIT to sham rTMS plus CBIT in a 1:1 ratio. The CBIT protocol is eight sessions over 10 weeks, once a week for 6 weeks and then biweekly. The rTMS protocol is 20 sessions of functional MRI-guided, low-frequency (1 Hz) rTMS targeted to the bilateral SMA over 5 weeks (weeks 2–6). MRI, clinical and motor assessments and neurophysiological evaluations including motor mapping will be performed 1 week before CBIT start, 1 week after rTMS treatment and 1 week after CBIT completion. The primary outcome measure is Tourette's symptom change from baseline to post-CBIT treatment, as measured by the Yale Global Tic Severity Scale. Secondary outcomes include changes in imaging, neurophysiological and behavioural markers.

Ethics and dissemination Ethical approval by the Conjoint Health Research Ethics Board (REB18-0220). The results of this study will be published in peer-reviewed scientific journals, on ClinicalTrials.gov and shared with the Tourette and OCD Alberta Network. The results will also be disseminated through the Alberta Addictions and Mental Health Research Hub.

Trial registration NCT03844919.

Strengths and limitations of this study

- ► Double-blind, sham-controlled repetitive transcranial magnetic stimulation (rTMS) trial in children with Tourette's syndrome.
- ► Combined therapy TMS plus comprehensive behavioural intervention for tics clinical trial for children with Tourette's syndrome.
- ► Precision-medicine treatment approach using functional MRI-guided rTMS targets in the bilateral supplementary motor area (individualised therapy).
- ► A limitation of this trial is the need to be physically located in Calgary, Alberta, Canada, to participate because the required neuroimaging and neurostimulation technologies are not yet portable.

INTRODUCTION

Background and rationale

Tourette's syndrome (TS) is a neurodevelopmental movement disorder characterised by repetitive movements and vocalisations called tics.[1] TS affects approximately 1% of school-age children across all cultures.[2 3] Tic severity predicts poor outcomes across physical, psychological and cognitive domains in youth, affecting quality of life at home, in school, with friends and family.[4 5] TS is typically associated with comorbid psychiatric conditions such as attention-deficit/hyperactivity disorder (54%), obsessive compulsive disorder (OCD; 50%), anxiety disorders (36%) and mood disorders (30%).[6] Many

children with TS have difficulties maintaining friendships, are bullied and teased, need individualised learning plans to accommodate tic expression in the classroom and require a significant portion of family resources to help manage their disorder.[7] This in turn can lead to lower educational attainment, poor employment outcomes and life-long difficulties maintaining relationships.

Neurobiological basis of Tourette's syndrome

TS is a complex disorder influenced by genetic and environmental factors. In particular, dysfunctional gamma-Aminobutyric acid (GABA) signalling may contribute to the impairment of the cortico-striato-thalamo-cortical brain circuit in TS, leading to involuntary behaviours (ie, tics).[8] Cortical excitability within the supplementary motor area (SMA), a major site for thalamocortical projections, has been linked to tic formation in TS.[9 10] Non-invasive in vivo measures using proton magnetic resonance spectroscopy (MRS) of localised GABA concentrations in the SMA indicate that increased control over motor outputs in TS (ie, suppression of tics) is due to increased GABAergic 'tonic' inhibition of the SMA.[11 12] Thus, the SMA poses a promising target site for neuromodulation interventions.

Current behavioural and medical interventions for Tourette's syndrome

There are currently two main approaches to treating TS: (1) non-pharmacologically and with (2) medication. First, Comprehensive Behavioural Intervention for Tics (CBIT), which is composed of awareness and competing response training, has demonstrated the highest efficacy of behavioural therapies, and is the primary recommended treatment for TS in adults and children over the age of 9 years.[13] Awareness training involves the detection of premonitory urges and/or early patterns that precede a tic and competing response training involves identifying behaviours that are physically incompatible with a targeted tic. The limitation of CBIT is age. Younger populations do not see the same benefit as adults due to a lack of self-awareness that is crucial for therapy.[14] Second, two classes of drugs widely used in TS are α2-adrenergic agonists and antipsychotics.[15] While both have been shown to be effective in treating tics, medications rarely eliminate all tics and may be associated with adverse side effects including weight gain,[16 17] drug-induced movement disorders,[18] sleep disturbance,[19] sedation[20] and increased blood pressure, heart rate and QT interval (as measured using an ECG).[21–23] Recommendation to use pharmacotherapy is only made when tics are so severe that the possible benefits outweigh the risks.[13] Children with TS have greater healthcare needs than those in the general population; however, they report receiving significantly less effective care.[24] One of the many issues families with TS often face is access to safe and effective therapy. While many physicians and psychologists know about habit reversal training for tics, very few know how to implement it.[25] Thus, many families that require treatment cannot access it.

Repetitive transcranial magnetic stimulation in Tourette's syndrome

An alternative to behavioural therapy and medications is neurostimulation. The number and range of neuropsychiatric disorders being treated by repetitive transcranial magnetic stimulation (rTMS) is ever growing.[26] Several small studies have suggested improvement in tic severity after rTMS for TS,[27–29] while others found no change.[30 31] These data were reviewed by Hsu *et al*.[32] This discrepancy may be due to small sample size, lack of sham controls, limited understanding of dosing and/or stimulation location. Our pilot study (NCT02356003)[33] of rTMS in children with TS used a novel targeting design of functional MRI (fMRI) for SMA targeting. The fMRI protocol was used to identify each participant's individual SMA location, which was then targeted bilaterally—1 cm lateral from midline into each hemisphere—to improve the likelihood of the TMS magnetic field reaching the target cortex. This pilot study showed significant improvements in tic severity in all participants (N=10, 8M, average age 11.52 years) after 15 sessions of low frequency (1 Hz) rTMS to the SMA (1800 stims/session). The average decrease in tic severity was 60.4% (range 38.1%–74.1%) as measured by the Yale Global Tic Severity Scale (YGTSS).[33] Limitations of this pilot study include the open design, small sample size and lack of follow-up: the effects may have been related to placebo response, and the durability of clinical effects were not assessed.

Objectives

Treatment options for children and adolescents with TS remain limited. Medications carry a side effect burden, and success of habit reversal therapy (HRT) techniques, as used in the highly recommended CBIT therapy, are predicated on a participant's awareness of their own tics. This is a limiting factor in children who may lack awareness due to their level of neurodevelopment. A targeted examination of plasticity, precision and pairing approaches will address this neurodevelopmental challenge. Low frequency rTMS to the SMA may mimic the brain's natural ability to suppress tics with age. Through neuroplasticity, rTMS may prime or modulate the brain to enhance CBIT effectiveness. The TITANS trial uses fMRI and neuro-navigated, robot-controlled rTMS to precisely target the SMA in TS children. Pairing these two safe treatments remains unexplored: we believe that pairing rTMS with CBIT will provide improved Tourette's symptom relief by inducing plasticity, retraining the brain to better suppress tics at an earlier age than usually expected.

We hypothesise that the treatment of active rTMS +CBIT in children with TS will result in a decrease in tic severity compared with sham rTMS +CBIT. We further hypothesise that active rTMS +CBIT will result in greater brain plasticity (table 1) than sham rTMS +CBIT.

Table 1 Secondary outcome measures for the TITANS trial including MRI and TMS data collection parameters

Outcome measure type	Secondary outcome measure	Data collection parameters
Changes in brain metabolite concentrations (SMA, dominant M1, and non-dominant M1)	GABA concentration	2.5×2.5×2.5 cm^3 voxel (bilateral SMA) and 2×3×4 cm^3 voxels (left and right primary motor areas): MEGA-PRESS protocol (TR=1.8 s, TE=68 ms, 14 ms editing pulses placed at 1.9 ppm and 7.46 ppm, 200 averages each).
	Glutamate concentration	2.5×2.5×2.5 cm^3 voxel (bilateral SMA) and 2×3×4 cm^3 voxels (left and right primary motor areas): PRESS protocol (TR=2000 ms, TE=30 ms, number of averages=64).
Changes in TMS neurophysiology measures (dominant M1 and non-dominant M1)	Short interval intracortical inhibition and intracortical facilitation	Measured with a suprathreshold test stimulus at 120% RMT given 2 ms (inhibitory) and 10 ms (facilitatory) after a subthreshold conditioning stimulus at 80% RMT using paired-pulse TMS.
	Long interval intracortical inhibition	Measured with a suprathreshold test stimulus at 120% RMT preceded 100 ms by a suprathreshold conditioning stimulus at 120% RMT using paired-pulse TMS.
	Cortical silent period	Measured at 120% RMT using single-pulse TMS while the participant contracts their FDI to 20% of their EMG-derived maximum voluntary contraction.
	Stimulus response curve	Average of 10 FDI MEPs evoked from six incrementing intensities (100, 110, 120, 130, 140 and 150% RMT) using single-pulse TMS.
Changes in TMS motor map measures (Dominant M1)	Motor map volume (resting and active)	Consists of the sum of the averaged MEPs at all the responsive grid points. This measure is thought to be a graphical indication of the total excitability of the cortical representation for the target muscle.
	Motor map area (resting and active)	Two-dimensional area encompassing all the responsive grid points. This measure is thought to represent the 'spread' of the corticomotor representation.
	Motor map centre of gravity (resting and active)	A spatial average of the corticomotor representation that is weighted by the amplitudes of the MEPs at each responsive grid point. This measure is used to define the position of TMS maps, and a shift in this location is suggested to identify changes in cortical representations of a muscle.

EMG, electromyographic; FDI, first dorsal interosseous; GABA, gamma-Aminobutyric acid; M1, motor area; MEGA-PRESS, Meshcher-Garwood point resolved spectroscopy; MEP, motor evoked potential; PRESS, point resolved spectroscopy; RMT, resting motor threshold; SMA, supplementary motor area; TE, time of echo; TMS, transcranial magnetic stimulation; TR, time of repetition.

METHODS AND ANALYSIS

Trial design

This is a phase II, single-centre, randomised, parallel group, sham-controlled clinical trial that will be held at the Alberta Children's Hospital (ACH) in Calgary, Alberta, Canada (figure 1). The trial will follow the Consolidated Standards of Reporting Trials guidelines[34] (figure 2). Participants will be randomised to either an (1) active rTMS +CBIT arm or (2) sham rTMS +CBIT arm in a 1:1 ratio using an algorithm that will stratify each participant by sex and age group (6–10, 11–14, 15–18 years). Sham-controlled TMS research is necessary to understand the neurobiological effects of TMS separate from placebo response. rTMS will be set up for either active or sham delivery in such a way that the participants, their families and all clinical evaluation raters will be blind to which group they are in: the two coils will be identical in appearance and produce similar auditory and scalp sensations. At week 36, there will be a brief follow-up consisting of TS symptom assessment to determine the durability of treatment effects.

Inclusion criteria

1. Between the ages of 6–18 years.
2. Primary diagnosis of TS (with possible comorbid conditions), measured by the Mini-International Neuropsychiatric Interview for children and adolescents (MINI-KID).[35]
3. Tourette's syndrome of moderate or greater severity at baseline, as measured by the YGTSS: total tic severity scores greater than 22 (or >11 if only motor or phonic tics).[36]
4. IQ greater than 80, as measured using the Wechsler Abbreviated Scale of Intelligence second Edition.
5. English fluency (to enable consent).
6. Medications for tics or psychiatric disorders are allowed if the dose has been stable for 6 weeks with adequate compliance, with a commitment to not change medication or dosage during the trial period.

Exclusion criteria

1. Diagnosis of mania or psychosis, as measured by the MINI-KID.[35]
2. Impediments to TMS or MRI (eg, implanted device, metal in the brain, pregnancy).
3. More than four previous HRT or CBIT sessions for Tourette's syndrome.

Informed consent

Parents and adolescents will provide written informed consent before participating in accordance with the Conjoint Health Research Ethics Board and Tri-Council

Time / Event	Baseline	CBIT Treatment										Post-Tx	Follow Up
			rTMS Treatment					Post-Tx					
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 36
CBIT		Intro	X	X	X	X	X		X		X		
rTMS (active or sham)			X	X	X	X	X						
Symptom Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments	X							X				X	
Imaging	X							X				X	
Motor Assessments	X							X				X	
Neurophysiology Testing	X							X				X	
Motor Mapping	X							X				X	

Figure 1 TITANS trial timeline. Outline of participant progression through the TITANS trial. At baseline (week 0) and post-treatments (weeks 7 and 11), participants undergo MRI, a battery of clinical assessments, symptom monitoring (Yale Global Tic Severity Scale and Modified Rush Video Rating Scale), transcranial magnetic stimulation (TMS) neurophysiology measures, motor assessment (Purdue Pegboard Task), and TMS motor mapping. Treatment consists of active or sham repetitive TMS (rTMS) for 5 weeks overlapped with simultaneous Comprehensive Behavioural Intervention for Tics (CBIT) therapy for 10 weeks. CBIT occurs on Mondays, weekly for the first 6 weeks then bi-weekly for a total of eight therapy sessions. rTMS treatment occurs 4 days a week (Tuesday to Friday) for 5 weeks (weeks 2–6). Symptom monitoring occurs every Friday (weekly). TMS tolerability is recorded with each TMS neurophysiology and motor mapping session, and weekly for rTMS sessions. Follow-up (Tourette's and mental health symptoms) occurs at week 36.

Policy Statement 2. Study staff will ask permission to share anonymised study data with collaborators for larger imaging analysis projects: this consent is voluntary and separate from the TITANS trial participation consent. No biological data (eg, blood, saliva or tissue samples) will be collected in this study. Consent will be obtained by the study principal investigator (PI) or research coordinator.

Patient and public involvement

Patients and the public were not involved in the design of the study.

Interventions

Eight sessions of CBIT will be delivered over 10 weeks, once a week for 6 weeks then biweekly.[37] The first two CBIT sessions will take approximately 90 min, with the following six sessions taking approximately 60 min. A trained CBIT therapist will use a private room to deliver the CBIT therapy to a participant, with or without a caregiver in the room (participant choice). The CBIT sessions will be video recorded to ensure inter-rater reliability between CBIT therapists.

Twenty sessions of rTMS (active or sham condition) will be delivered four times a week for 5 weeks: low-frequency (1 Hz), 100% resting motor threshold (RMT), fMRI and neuronavigated TMS to the participant's bilateral SMA, 1800 stimulations (active) or clicks (sham) per session. Participants will take breaks throughout the TMS sessions as needed, and therefore each TMS session will take 30–60 min. A weighted blanket, footrest, earplugs, neck, back and lap pillows will be available for participant comfort. TMS sessions will be video recorded once a week to assess tic expression during TMS.

Figure 1 outlines the time schedule of participation including baseline assessments (week 0), CBIT treatments (weeks 1–6, 8 and 10), rTMS treatments (weeks 2–6), post-TMS assessments (week 7), post-CBIT assessments (week 11) and follow-up (week 36).

Criteria for discontinuing or modifying interventions

Non-compliance, defined as missing ≥2 CBIT sessions or ≥2 rTMS sessions, without a desire/ability to make-up the missed sessions, may result in removal from the study. In addition, participation will be terminated if a participant experiences (1) a serious adverse reaction (eg, seizure), or (2) complications or severe worsening of symptoms (clinical judgement of TP and AK). Participants may withdraw from the study at any time.

Strategies to improve adherence

This study includes 28 intervention visits over 10 weeks of time: every effort will be made to book appointments at times that work best for participant families (eg, before or after school). Participants can choose to watch movies or listen to music during the TMS visits, and they can choose to do an activity (eg, draw, colour, build puzzles) during CBIT visits. Study staff will ask participants about their CBIT homework during TMS sessions to improve adherence of CBIT practice between therapy sessions.

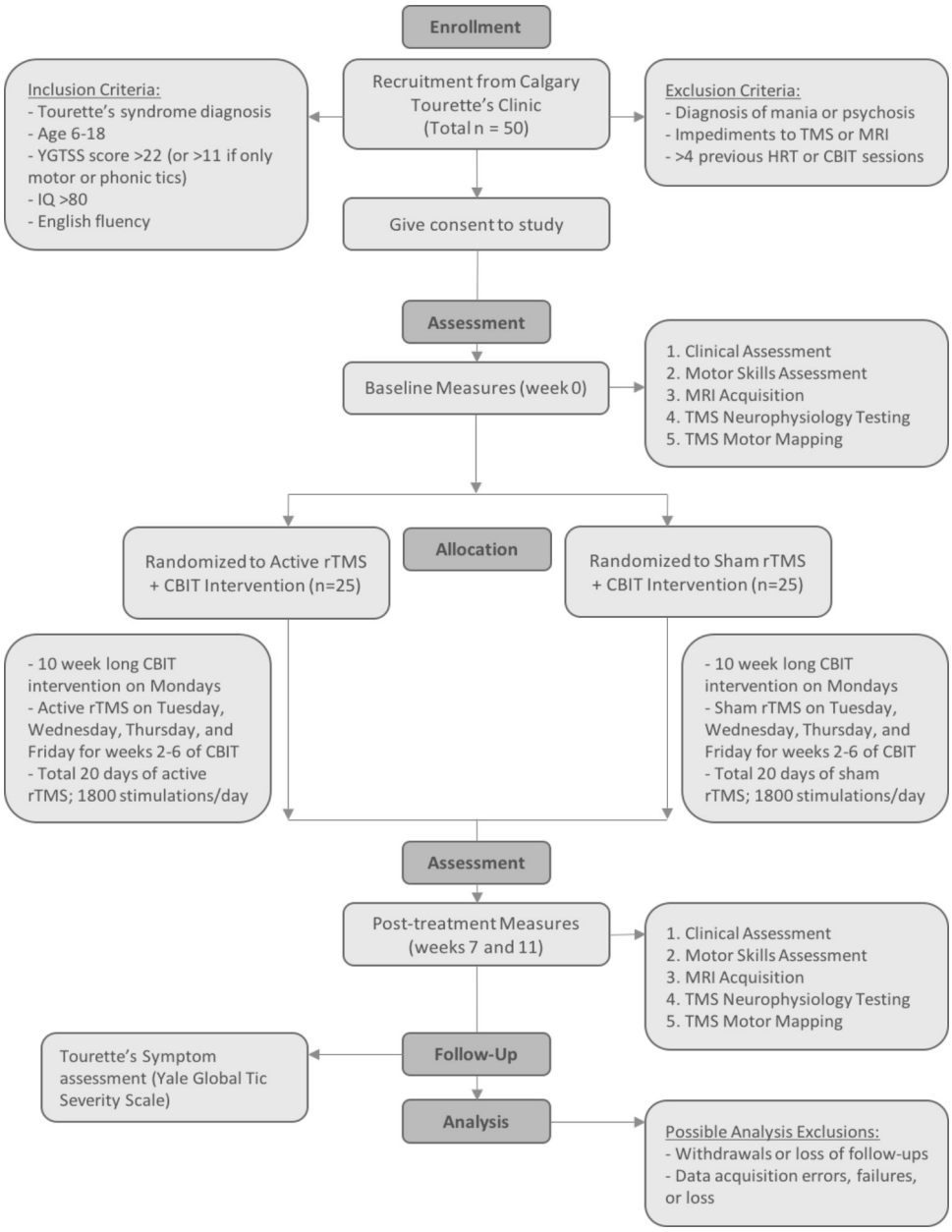

Figure 2 Study flow diagram. Consolidated Standards of Reporting Trials diagram showing the flow of participants through each stage of the TITANS clinical trial: phase II single centre, randomised, parallel group, double-blind sham controlled rTMS trial in children with moderate-to-severe Tourette's syndrome. CBIT, comprehensive intervention for tics; HRT, habit reversal therapy; rTMS, repetitive; TMS, transcranial magnetic stimulation; YGTSS, Yale Global Tic Severity Scale.

Relevant concomitant care

Medications for tics or psychiatric disorders are allowed if the dose has been stable for 6 weeks with adequate compliance and a commitment to not change the medication dosage during the trial period. Therapy other than HRT or CBIT for tics or psychiatric disorders is also allowed. Participants cannot participate in other neurostimulation or habit reversal type therapies during the trial period. These will be recorded and reported in any subsequent publications.

No direct post-trial care is offered, but participants can obtain their personal data from study staff to share with other health providers and/or educators if they choose. If a participant suffers harm during the study, they have legal rights to seek damages: no direct compensation will be provided by the researchers, funding bodies, the University of Calgary or Alberta Health Services.

Outcomes

The primary outcome is Tourette's symptom change (YGTSS) from baseline to post-CBIT treatment. Secondary outcomes include changes in (1) imaging, (2) neurophysiological and (3) behavioural markers (tables 1 and 2). First, magnetic resonance images will be obtained at baseline, post-TMS and post-CBIT on a GE 3T Discovery 750 W MRI scanner. Proton magnetic resonance imaging

Table 2 Description, time of delivery and proposed analyses of behavioural and motor assessments for the TITANS trial

Measure type	Measure	Description	Time	Analyses (week 0–11)
Diagnosing and functioning assessments	Mini International Neuropsychiatric Interview for Children and Adolescents	Brief structured diagnostic interview assessing psychiatric disorders and suicidality in children aged 6–17 years.	Week 0	Not applicable
	Wechsler's Abbreviated Scale of Intelligence second Edition	Measure that assesses intellectual functioning of individuals aged 6–89 years.	Week 0	Not applicable
	Paediatric Quality of Life	Child self-report and parent-proxy-report scale measuring health-related quality of life in children and adolescents aged 2–18 years.	Weeks 0, 7, 11	Mean, SD, range; paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions
	Modified Stanford Expectation of Treatment Scale	Scale that measures positive and negative treatment expectancies and sham vs active treatment prediction.	Weeks 0, 7	Mean, SD and range for positive and negative expectancy (week 0); proportion of participants who correctly guess active/sham condition (week 7)
Tourette's syndrome symptom assessments	Yale Global Tic Severity Scale	Tic severity scale assessing number, frequency, intensity, complexity and interference of motor and vocal tics.	Weeks 0, 2, 3, 4, 5, 6, 7, 11	Paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions
	Modified Rush Video Scale	Video-based objective rating scale of tics to assess number of body areas, frequency and severity of tics.	Weeks 0, 7, 11	Paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions
Co-morbidity symptom assessments	Children's Yale-Brown Obsessive-Compulsive Scale	Scale used to assess juvenile obsessive-compulsive disorder.	Weeks 0, 7, 11	Paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions
	Conners 3	Scale used for measuring attention deficit/hyperactivity disorder and associated problem behaviours.	Weeks 0, 7, 11	Repeated measures analysis of variance with group (active, sham) as the between-subjects factor
	Multidimensional Anxiety Scale for Children second Edition	Measure for assessing anxiety symptoms in children.	Weeks 0, 7, 11	Paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions
Hand motor assessments	Edinburgh Handedness Questionnaire	Common measure for assessing handedness and hand dominance.	Week 0	Not applicable
	Purdue Pegboard Task	Task for measuring gross arm and fine finger movements and dexterity.	Weeks 0, 7, 11	Mean, SD, range; paired t-test within subject; one-tailed two-sample t-test of within subject changes between active and sham conditions

(MRS) will be used to determine metabolite concentrations in voxels placed in the SMA ($2.5\times2.5\times2.5\,cm^3$), left and right primary motor areas ($2\times3\times4\,cm^3$) using anatomical markers and an fMRI finger-tapping task as a guide. Changes in glutamate and GABA will be assessed from baseline to post-TMS and post-CBIT treatments: as an inhibitory neurotransmitter,[12] we expect an increase in GABA concentration to correlate with reduction in tic symptom severity. Second, neurophysiological testing will be performed using a handheld figure-eight flat iron TMS coil (Magstim) to determine stimulus response curve,[38] cortical silent period,[39 40] short interval intracortical inhibition and facilitation[41 42] and long interval intracortical inhibition[43] at baseline, post-TMS and post-CBIT to measure changes in excitability and inhibition of corticospinal, intracortical and interhemispheric motor networks.[44] Resting and active motor maps of the dominant hand area using robotic TMS (figure-eight airfilm coil, Magstim) will measure two-dimensional area, three-dimensional volume, hotspot location and size and centre of gravity of the dominant hand motor area[45–48] at baseline, post-TMS and post-CBIT as a potential measure of motor control change. Motor mapping has been shown to be feasible in Tourette's syndrome.[49] Given, its novelty, motor mapping will be exploratory. Third, behavioural symptoms will be measured with the Conners-3 parent rating scale,[50] Children's Yale-Brown Obsessive-Compulsive Scale,[51] Multidimensional Anxiety Scale for Children[52] and Paediatric Quality of Life (PedsQL)[53] at baseline, post-TMS and post-CBIT treatments. Tic symptom severity will be measured once a week during the TMS treatment weeks using the YGTSS and a video assessment. YGTSS and the Modified Rush Video Scale[54] will be conducted at baseline, post-TMS and post-CBIT

treatment to thoroughly quantify tic expression change with treatment. We hypothesise greater tic reduction in the active rTMS +CBIT treatment arm compared with sham rTMS +CBIT treatment.

Sample size

The sample size was estimated with G*Power (V.3.1.9.4).[55] Prior pilot rTMS data (n=10) and a previous randomised controlled CBIT study (n=126) informed the estimates of effect size. Piacentini *et al*[37] reported a mean difference of 4.1 (95% CI, 2.0 to 6.2) and a standardised mean difference of 0.7 in total YGTSS scores between a CBIT and control group.[37] We expect the added effect of rTMS to be of the same magnitude, and thus we expect to see a difference in change of at least 4.1 between rTMS plus CBIT compared with CBIT alone. We estimate the SD of change to be 5.85 based on the reported Cohen's d of 0.7. We will use the Benjamini-Hochberg approach to adjust alpha, with a false discovery rate of 5% and a minimum power of 80%. We assume a potential data loss of 20% due to withdrawal, loss of follow-up, data acquisition failures/errors and so on. With this difference of 4.1 and SD of 5.85 our ideal sample size calculation is 31 per group (62 total), 80% power. However, the funding received for this study allows for n=25 per group (50 total): with 25 per group, as long as the SD of pre to post change is not bigger than 5.31 (alpha (α)=0.033 as per Benjamini-Hochberg), we will still be powered to detect a desired 4.1 change. In addition, 20 participants per group (due to potential data loss/drop out) is still powered to detect a 4.1 difference as long as the SD of the pre to post change is not bigger than 4.73 (α=0.033).

Participants will be recruited through the Calgary Tourette's Syndrome Clinic (ACH, Calgary, Alberta—led by TP), a network of paediatricians, TS families and advertisements.

Assignment of interventions: allocation

Participants will be randomly assigned into either active or sham rTMS plus CBIT in a 1:1 ratio. The sequence will be generated with random sized blocks of 2, 4 and 6, and use the Research Electronic Data Capture (REDCap) randomisation module for recruiters to access subject allocation. The algorithm will stratify by sex and age group (7–10, 11–14, 15–18 years). On allocation, a participant ID will be generated for each participant to allow for blinded analysis. An unblinded TMS specialist that is not involved in clinical assessments or symptom monitoring will set up the rTMS coil for active or sham delivery.

Assignment of interventions: blinding

Participants, their parents and all raters responsible for clinical evaluation will be blind to group status. Blinding will remain in effect until study completion through the anonymised participant ID, and separation of clinical and randomisation data: only AN-A and the TMS specialists responsible for TMS treatment coil set-up will be unblind to treatment condition.

The only time unblinding may occur is if a safety concern has arisen. This includes any adverse event or significant intolerability that results in participant drop-out. AN-A would be responsible for unblinding and communicating allocation with necessary providers.

Data collection and management

Assessment data will be collected by trained study staff (table 2). On trial initiation, or addition of new staff members, two raters will complete clinical assessments simultaneously to determine inter-rater reliability (minimum n=2). Data from TMS neurophysiology and motor mapping measures will be analysed throughout the study period to ensure quality data collection.

To promote participant retention, participants and their families will receive an educational tour of research space, including the opportunity to go inside a mock MRI scanner and feel TMS stimulations. The schedule and reasoning of study visits will be thoroughly explained prior to study enrolment, and therefore we expect very high retention rates. In fact, we expect a compliance of 99% based on a recently completed open trial of rTMS in youth with treatment-resistant depression conducted by our laboratory.[56] Deviations from the standard study protocol (eg, rescheduling a CBIT or rTMS visit due to illness) will be thoroughly documented in paper and electronic databases.

Clinical assessment data will be entered and stored in REDCap, with data exported to excel after participant completion for secondary electronic data storage. REDCap requires two-factor authentication and Excel databases will be password protected. All assessments can be completed electronically by participants and parents for self-report and parent-report respectively through the REDCap survey feature. Paper assessment data will be stored in locked filing cabinets, and only the informed consent form will contain the participant's name: all other assessments are anonymised by participant ID, including REDCap and excel databases. Imaging data are labelled with participant ID when collected (not name) and stored on secure servers (password protected). TMS assessment data are also labelled with participant ID when collected and stored on secure servers. All assessment data are anonymised by participant ID and is only accessible by study staff involved in data collection or analysis.

Statistical methods

Our primary outcome is Tourette's symptom change (total YGTSS score) from baseline (week 0) to post-treatment (week 11): within-subject changes will be calculated using a paired t-test to determine changes in YGTSS scores within each group (α=0.017; determined using a Benjamini-Hochberg approach). With these change variables we will conduct a one-tailed two-sample t-test of within subject changes between the active and sham rTMS treatment arms (α=0.033). If data violate assumptions, we will use the Wilcoxon rank-sum test (non-parametric approach). Our secondary outcomes look at metabolite

concentration and neurophysiology measure changes from baseline (week 0) to post-treatment (week 11): two-tailed two-sample t-tests of the within subject changes will be conducted for imaging and neurophysiology measures (weeks 0–11). Change across time (comparing weeks 0, 7 and 11) is an exploratory outcome of this study that will use a linear mixed effects model with time, group and time-by-group interaction as fixed effects and participant as random effect.

Data from participants who withdraw from the study, voluntarily or due to non-compliance, will not be included in statistical analyses. The Last Observation Carried Forward Method will be used if data are missing between weeks 1 and 10. Finally, no interim analyses are planned: stopping the entire trial will be a consideration if two or more significant adverse events (eg, seizure) occur, and the study neurologists (AK and TP) will advise such a decision.

Participant safety

MRI technologists will assist in ensuring safe MRI protocols (ie, no metal in scan area, ear protection during scan). TMS procedures will be performed by experienced staff trained in management of potential adverse events. There is a very small risk of seizure associated with TMS, reported primarily in people with pre-existing seizure disorders: the seizure incidence with TMS is estimated at ~0.01%–0.1% compared with 0.07%–0.09% spontaneous incidence in the general population.[57] Safety and tolerability scales will be used to monitor TMS safety. Brief discomforts such as headache, neck pain or tingling in the hands are sometimes reported: these are usually rated as mild and typically disappear on their own within an hour of TMS completion. Our academic paediatric centre has obtained standardised safety and tolerability data from paediatric participants using both hand-held and robotic TMS, and over 3.5 million TMS stimulations were shown to be safe and well-tolerated in children.[58]

If an adverse event of sufficient magnitude occurs, the parent will be offered support to take the child to the emergency department or home. The PI will be responsible for reporting serious adverse events and any unanticipated problems to the local research ethics board. The study statistician (AN-A) will prepare reports that list adverse events, serious adverse events and disorder-specific or treatment-specific events required to ensure good clinical care, and to identify emerging trends.

Participation will be terminated under the following conditions: (1) if serious adverse reactions occur (eg, seizure), (2) serious complications or severe worsening of symptoms (clinical judgement of TP and AK), (3) if a participant needs or wants to withdraw from the study and (4) if the participant is not cooperative or physically unable to take part in the study (eg, RMT is greater than TMS machine output ability).

Oversight and monitoring

In accordance with Good Clinical Practice Guidelines, the Trial Steering Committee will manage the trial: all lead investigators of this paper (FM, AK, TP and GW) are steering committee members. The Trial Management Committee (CKK, RS, SC and FM) are responsible for day-to-day running of the trial, and the Data Safety Monitoring Board are responsible for safeguarding the interests of trial participants, potential participants and investigators (EZ and AN-A).

This study does not have a data monitoring committee. The investigative team, particularly the study coordinator, will be responsible for ensuring data are complete and accurately entered. Inter-rater reliability will be performed for assessment protocols, and integrity ratings will be made on 10% of CBIT sessions via video recording akin to Piacentini *et al*.[37] Protocol modifications will be approved by the local research ethics board and logged on ClinicalTrials.gov. When appropriate, changes will be communicated to participants (eg, a change in assessment tool or study timeline). The study is supported by grant funding, which plays no role in data monitoring or auditing.

ETHICS AND DISSEMINATION

This project was approved by our local research ethics board (Conjoint Health Research Ethics Board at the University of Calgary).

We will publish our findings in peer-reviewed scientific journals. We will report results on ClinicalTrials.gov, and we will share results with the Tourette and OCD Alberta Network (a non-profit that works with TS patients and their families).[59] We will also report results through the Alberta Addictions and Mental Health Research Hub, which works with policymakers, people in healthcare operations, clinicians, researchers and people with lived experience. A participant can request their individual data.

We do not have plans to grant identifiable data to the public due to ethics board regulations and provincial legislation, but aggregate and de-identified data are available on request. Specific statistical code is also available on request. The full protocol is published here.

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Contributors CKK: design of the study, writing, critical revision, transcranial magnetic stimulation, magnetic resonance spectroscopy, functional MRI, motor mapping, neurophysiology measures, motor skill assessment and analysis. RS: design of the study, writing, critical revision, MRI, transcranial magnetic stimulation, data management, recruitment and analysis. AK: conception and design of the study, critical revision, transcranial magnetic stimulation and neurology. TP: conception and design of the study, recruitment and neurology. GW: design of the study and comprehensive behavioural intervention for tics. EZ: design of the study and transcranial magnetic stimulation. AH: design of the study and magnetic resonance spectroscopy. AN-A: design of the study, blinding, randomisation, statistical design and analysis. PEC: conception and design of the study, transcranial magnetic stimulation and psychiatry. SC: comprehensive behavioural intervention for tics, functional MRI, transcranial magnetic stimulation, recruitment and analysis. FM: principal investigator, conception and initiation, running of the trial, writing, critical revision and final approval of the manuscript. All authors have read and approved the final manuscript.

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Competing interests FM, CKK, RS, AK, TP, GW, EZ, AH, AN-A and SC have no conflicts of interest. PEC has received research grant support from the National Institute of Mental Health, Brain and Behavior Research Foundation and Pfizer. He has received equipment support from Neuonetics and received supplies and genotyping services from Assurex Health for investigator-initiated studies. He is the primary investigator for a multicentre study funded by Neuronetics and a site primary investigator for a study funded by NeoSync. PEC is a consultant for Procter & Gamble Company and Myriad Neuroscience.

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