STUDY IDENTIFICATION

Project title	Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot
Short title	MNS pilot
IRB	Washington University Human Research Protection Office
IRB title	Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot
IRB ID #	202011092
Grant support	The Washington University Institute of Clinical and Translational Sciences (NIH CTSA grant UL1TR002345).
Grant title	Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot
IDE status	Non-significant risk device study
ClinicalTrials.gov Identifier	NCT04731714
Protocol version (revision date)	Version 20220120 (January 20, 2022)

OBJECTIVES

Chronic tic disorders (CTD), including Tourette syndrome (TS), are associated with a substantially reduced quality of life [1]. Medication treatments are no more than 50-60% effective in RCTs, and are often discontinued due to unacceptable side effects [2]. Behavioral therapies require ability to participate in therapy and a specially trained therapist [3], but weekly visits to psychologists are impractical for many Americans, especially in rural areas [4]. Patients strongly desire new treatment options [5].

In June, 2020, Stephen Jackson's group at the University of Nottingham published a fascinating report in **Current Biology** on a potential novel treatment for tics [6]. The radical new idea arose from observations associating movement inhibition with 8-14 Hz activity in motor cortex. They first showed that rhythmic 12 Hz peripheral stimulation of the median nerve evoked synchronous contralateral EEG activity over primary sensorimotor cortex, whereas arrhythmic stimulation at the same mean rate did not. As hypothesized, median nerve stimulation (MNS) at 12 Hz created small but statistically significant effects on initiation of voluntary movements. Importantly, they also demonstrated that this stimulation did not meaningfully impair concentration, suggesting that the effect did not operate through simple distraction. They went on to test 10 Hz MNS in 19 TS patients, and demonstrated using blinded video ratings a significant reduction in tic number and severity during 1-minute stimulation epochs vs 1-minute no-stimulation epochs. They noted that in some participants, benefit lasted beyond the end of the stimulation epoch [*personal correspondence*]. Videos accompanying the publication showed dramatic benefit during MNS in some subjects. Although the authors appropriately noted the steps needed to generalize these results to clinical practice, news reports already have led a number of TS patients to contact them asking for treatment. The Nottingham group has referred such inquiries from the U.S. to me as leader of our Wash.U. Tourette Association of America (TAA) Center of Excellence.

We hypothesize that the tic benefits reported by our Nottingham colleagues are replicable, that they are specific to rhythmic stimulation, which alone entrained cortical activity, rather than to a placebo effect, and that they endure past the end of stimulation.

Here we propose (a) to replicate the Nottingham findings using identical methods, and (b) to test rhythmic MNS against a placebo treatment (arrhythmic MNS at the same mean frequency). At the same time, we will gather additional preliminary data needed for a future R01 application, including response and tolerability with longer (5-minute) stimulation blocks, and the duration of benefit after the end of a stimulation block.

Aim 1. Replicate the Nottingham MNS results in a new sample of people with TS. We have been in frequent contact with the Nottingham group to ensure that we can match their methods.

Aim 2. Test the hypothesized electrophysiological mechanism and rule out a placebo effect as cause for the symptomatic benefit, using randomized allocation of rhythmic stimulation to a control condition, namely random (not rhythmic) stimulation.

Aim 3. Gather additional preliminary information for a future clinical efficacy trial and NIH grant application. This information will include (a) the duration of effect after the end of stimulation, which is crucial information for designing chronic treatment, and (b) preliminary information on individual

characteristics that predict improvement with simulation, e.g. demographics, tic severity, premonitory urges, sensory hypersensitivity, ADHD, tic suppression ability, and tic phenomenology.

Completion of these Aims will give a clear go/no-go signal for a future clinical trial of chronic MNS delivered by a portable, wristwatch-style device.

STUDY DESIGN

Overall study timeline

The study will complete enrollment within 11 months and complete all human subjects procedures within 1 year.

Overview of each subject's participation

First we screen potential participants to ensure they meet criteria for study enrollment, and characterize their symptoms and other demographic and clinical features. They then participate in 2 stimulation sessions, at least a week apart, which are identical except that one session uses rhythmic and one uses arrhythmic MNS with the same number of total pulses per minute. Session order is randomized and participants are blinded to order. (Biological carryover effects are very unlikely.) Tics before, during and after stimulation epochs are video recorded for later analysis blind to time, stimulation (on *vs.* off), and stimulation type (rhythmic *vs.* arrhythmic).

Recruitment

Sources may include clinical referrals, online advertising, and word of mouth. We will also involve the local chapter of the Tourette Association of America, which is a key part of our TAA Center of Excellence

Prior to first visit

1. REDCap presents an informed consent document to parents of potential child participants explaining the study, risks and benefits of participation and that participation is voluntary. The ICD will be provided online prior to the in-person visit. Adult participants will provide their own informed consent. For child participants, consent from one parent or guardian is sufficient, as the study is minimal risk. Children must assent to participate.
2. Participants may optionally consent to share video of their tics and response to stimulation with the general public (as did some participants in the **Current Biology** report [6]).
3. REDCap provides questionnaires online prior to the visit, after the participant (and guardian) review the ICD. These include:
    a. Age, sex
    b. Self-reported race and ethnicity
    c. Handedness (Edinburgh Handedness Inventory)
    d. Health history
        i. Medical history
        ii. Family history of tics and related symptoms
        iii. Treatment history: Lifetime neurosurgery, lifetime adequate behavior therapy for tics or OCD, changes in treatment within the past 2 weeks, plans to change treatment between the 2 stimulation visits

iv. Current treatment

e. TS symptom history
    i. Lifetime tic list reported by participant or parent (list from Yale Global Tic Severity Scale [YGTSS]) [7]

f. Current symptom status
    i. Past week tic list from the YGTSS
    ii. Adult Tic Questionnaire (ATQ) tic rating [8,9]
    iii. Premonitory Urge for Tics Scale (PUTS) [10]

g. Other / comorbid symptoms
    i. Self-rated current Y-BOCS [11]
    ii. Self-rated current ADHD Rating Scale [12]
    iii. Quantitative autistic traits by Social Responsiveness Scale (SRS-2) [13]

First visit

1. Potential subjects will review the informed consent document with the investigator or designee and will have opportunity to resolve questions or concerns. The investigator will document that a child understands the procedures and assents.
2. We review the online questionnaires and collect the following additional measures:
    a. TS symptom history
        i. Diagnostic Confidence Index [14]
    b. A TS clinician will review the history with the participant and perform a neurological and psychiatric examination as appropriate.
    c. Current symptom status
        i. YGTSS, performed by expert clinician
        ii. 5-minute observation, staff in room quiet, to count tics at baseline [*performed during "stimulation protocol," below*]
    d. Disease-related outcome data, healthcare utilization, and global functioning
        i. "Marked distress" or impairment in a life role: ever, and in the past week (clinical judgment)
    e. Tic disorder diagnosis by DSM-5, DSM-IV-TR and DSM-IV
3. Proceed to "stimulation protocol"

Stimulation protocol

See MNS section below for technical details on all procedures

1. Clean skin at right wrist. Apply conductive gel.
2. Attach electrodes (so they're visible in the baseline video for optimal blinding).
3. Check resistance through electrodes. If < 100 Ω, look for a short and correct it. If resistance remains out of range, do not proceed without specific approval from PI. Record resistance.
4. Optional but recommended bathroom stop
5. Procedures below are performed in a quiet room with only participant and study staff present but not conversing
6. All videos are recorded from the elbows up for later blinded ratings of tics
7. 5-min video-recorded baseline session, also rated live at the first visit to record baseline tic

frequency

8. At this point, the PI or designate will review the inclusion and exclusion criteria (including mean baseline tic frequency ≥ 1/min.) and document eligibility for the study before additional procedures
9. Determine stimulation threshold for a train of 8 pulses (12 Hz, pulse width 200μs), starting at 1mA and increasing until a twitch of the thumb is seen, to a maximum of 20mA (expected range 2-15 mA, *personal communication, B. Morera Maiquez to KJB*). Some subjects may wish to withdraw at this point if suprathreshold stimulation is too uncomfortable, but in the Nottingham report, participants age 15 and up found the stimulation tolerable. Since electrode placement can change slightly between visits, on the second visit the threshold is verified and adjusted as needed. We record the threshold at each visit.
10. Resume video recording
11. Synchronize clocks for video, urge rating software, and stimulation
12. MNS stimulation on or off blocks as follows, without planned breaks (total 29-44 min.)
    a. Two 1-min. blocks of MNS on and two 1-min. sessions off, the order of these 4 sessions randomized (*this design matches the Nottingham study*)
    b. 5-min. block MNS off
    c. 5-min. block MNS on
    d. 5-min. block MNS off
    e. 5-min. block MNS on
    f. 5-minute stimulation **off** blocks until tics return to baseline frequency (min. 1 block, max. 4 blocks)
13. Stop video recording
14. CGI-I (Clinical Global Impression of Improvement) rating for tics by participant and investigator
15. Debrief
    a. ratings of tic improvement and discomfort using the CGI Efficacy Index
    b. ask for comments on benefit, tolerability, side effects
    c. participant and staff guess whether this was active or control stimulation day (*to test adequacy of blinding*)
    d. ask if they think they would use a portable stimulator
16. First visit: confirm scheduling for second visit

Prior to second visit

1. Participants repeat the following measures online:
    a. Health history
        i. Change in medical history since first visit
        ii. Current treatment
    b. Current symptom status
        i. Past week tic list from the YGTSS
        ii. Adult Tic Questionnaire (ATQ) tic rating [8,9]
    c. Other / comorbid symptoms
        i. Self-rated current Y-BOCS [11]

ii. Self-rated current ADHD Rating Scale [12]

Second visit

1. We review the online questionnaires and collect the following additional measures:
    a. TS symptom history
        i. Diagnostic Confidence Index
    b. Current symptom status
        i. YGTSS, performed by expert clinician [7]
        ii. 5-minute observation, staff in room quiet, to count tics at baseline [*performed during "stimulation protocol"*]
    c. A TS clinician will review the history with the participant and perform a neurological and psychiatric examination as appropriate.
    d. Disease-related outcome data, healthcare utilization, and global functioning
        i. "Marked distress" or impairment in a life role: past week (clinical judgment)
        ii. Record any change in treatment since the first visit
    e. Tic diagnosis by DSM-5, DSM-IV-TR and DSM-IV
2. Proceed to "stimulation protocol"

MNS procedure

We will apply square-wave 200 μs pulses triggered by computer at the threshold for thumb movement (expected ~2-15mA) to surface electrodes over the median nerve at the right wrist (conductive gel, 30 mm apart center-to-center, anode distal).

Video analysis

An investigator blind to treatment order (rhythmic MNS first or second), stimulation condition (on *vs.* off), visit number, and order (of the 1-minute or 5-minute blocks) uses a derivative of our TicTimer Web software [15,16] to mark each occurrence of any tic and to provide a rating of tic severity for the full 5-minute block or (for the 1-minute blocks) for each tic occurrence.

Subject payments

Subjects will receive $15 or the equivalent value on a gift card at the end of the first visit, and an additional $25 at the end of the second visit, to help compensate for their loss of time. Travel costs to study visits may be reimbursed.

Clinical *vs.* research purposes

All procedures in this study are done for research purposes.

POTENTIAL RISKS

(*The language below, in this section, is addressed to the patient, as in an informed consent document.*)

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. You will be told of any new information that may affect your willingness to participate in this study. Dr. Black will answer any questions you have about these risks.

MNS

Likely:

- Discomfort in the forearm, wrist or hand during active stimulation
- Mild skin irritation from applying or removing the surface electrodes

Other study procedures

Likely:

- The questionnaires and interview may be slightly boring, fatiguing or challenging.
- The video recordings may be slightly boring

Rare:

- The questions that you are asked during this study could make you feel uncomfortable. If any question makes you feel uncomfortable, you may choose not to answer it.
- Confidential information about you may be accidentally disclosed. However, we think the risk of accidental disclosure is small. The information we gather during the course of the study is coded only by a study number and is kept separately from your name, address, etc.

LOCATIONS / SITES OF STUDY

Data collection: Washington University in St. Louis

Data analysis: Washington University in St. Louis

STUDY DURATION

Anticipated duration of entire research activity per participant:

- 2-4* days, usually over the course of 1-2 weeks

* Planned participation includes a screening visit followed by two stimulation sessions, the first of which may occur on the same day as the first stimulation session. The maximum of 4 days rather than 3 allows one additional make-up MNS session for each participant in the event of technical problems that prevent completion of the procedures.

Anticipated duration of entire research activity:

One year

SAMPLE SIZE

N = 32 (study completers)

Power considerations

We can estimate variance from the Nottingham tic frequency results. Fig. 5 in ref. [6] shows the SD of the improvement in tic frequency between the MNS on and off conditions to be ~81 (total tics per condition). The mean difference between conditions was ~41, corresponding to a nearly 30% mean decrease in tic frequency. A 25% decrease in tic severity using the YGTSS Total Tic Score (TTS) is highly predictive of *clinically meaningful* clinical improvement [17], and the TTS is highly correlated to tic frequency on video recordings [18,19].

From these data, a sample size of 32 will have 81% power to find a statistically significant result for Aim 1 (two tails) assuming the population mean response is the 30% reported by our colleagues in Nottingham. This sample size provides 75% power to detect clinically meaningful (−25%) improvement (one tailed).

Estimating screen failures and dropouts at a total rate of 27%, we will plan to enroll up to 44 participants to arrive at 32 who complete the entire study.

INCLUSION CRITERIA

Inclusion criteria for all subjects:

- Age 15-64 inclusive at initial screening visit
- Informed consent by adult subject; assent by child and informed consent by guardian
- Current DSM-5 Tourette's Disorder or Persistent (Chronic) Tic Disorder
- At least 1 tic per minute (average) during the first 5-min. baseline video session on the first visit (as scored during the session by the investigator)

EXCLUSION CRITERIA

Exclusion criteria for all subjects:

- Unable to complete study procedures for any reason
- Has an implanted device that could be affected by electrical current
- Pregnancy known to participant or (for children) to the parent
- Known or suspected primary genetic syndrome (*e.g.* Down syndrome, Fragile X)
- Intellectual disability (known, or likely from history and examination)
- Head trauma with loss of consciousness for more than 5 minutes
- Significant neurologic disease, not counting TS (exceptions include febrile seizures or uncomplicated migraine)
- Severe or unstable systemic illness
- Factors (such as exaggerated signs) that in the judgment of the principal investigator make the video recording or YGTSS an inaccurate assessment of tic severity
- Judged by investigator to be unlikely to complete study procedures or to return for later visits
- Change in somatic or psychotherapeutic treatment in the 2 weeks preceding the first stimulation visit
- Planned change in somatic or psychotherapeutic treatment between the 2 stimulation visits

CONCOMITANT MEDICATIONS

Required: none

PROHIBITED MEDICATIONS

none

TREATMENTS AND DOSAGE

Rhythmic

- 10 Hz for 1-minute epochs (to replicate **Current Biology** report)

- 12 Hz for 5-minute epochs

Arrhythmic

- Same number of pulses per minute as in the rhythmic condition, but with a random inter-pulse interval, as implemented by the Nottingham group in the **Current Biology** report

Both

- Square-wave 200 μs pulses triggered by computer at the threshold for thumb movement (expected ~2-15mA) to surface electrodes over the median nerve at the right wrist (conductive gel, 30 mm apart center-to-center, anode distal)

ANALYSIS PLAN/APPROACH/METHODOLOGY

Outcome measures

The primary outcome measures are derived from audiovisual recordings (head to elbows), later broken into 1-min. or 5-min. clips, then rated in random order by an experienced movement disorders physician blind to stimulation conditions (on vs. off, rhythmic vs. arrhythmic) and order (rhythmic at first or second visit), who will record tic frequency and rate severity. For the 1-min. MNS on/off blocks, severity is rated on a 5-point scale (from the YGTSS severity item) for each occurrence of any tic, to replicate the methods of the Nottingham group. For the 5-min. blocks, overall tic severity is rated on the same scale once for each 5-min. block. This choice dramatically reduces rater time without sacrificing validity. Analysis for each participant can begin after his/her second stimulation visit is complete and all other data from that participant is checked.

Primary Outcome Measures:

1. Change in tic frequency compared to when MNS is off
   An expert rater blind to condition and time point assesses the number of tics per minute. A one-tailed t test will compare mean tic frequency in the last 40 s of on *vs.* off 1-minute stimulation epochs on the rhythmic MNS day. This analysis replicates that of Study 3 in the Morera Maiquez et al 2020 citation. A secondary analysis will test for carryover effects.
   [Time Frame: During rhythmic MNS stimulation]

2. Change in tic severity compared to when MNS is off
   Severity is rated on a 5-point scale for each occurrence of any tic. The scale is the Intensity item from the Yale Global Tic Severity Scale [YGTSS], which uses integer scores from 0 (no tics) to 5 (severe intensity). A one-tailed t test will compare mean tic severity in the last 40 s of on *vs.* off 1-minute stimulation epochs on the rhythmic MNS day. This analysis replicates that of Study 3 in the Morera Maiquez et al 2020 citation. A secondary analysis will test for carryover effects.
   [Time Frame: During rhythmic MNS stimulation]

3. Change in tic frequency during rhythmic MNS (vs. arrhythmic MNS)
   An expert rater blind to condition and time point assesses the number of tics per minute. Change in tic frequency from baseline (stimulation off) is compared between 5-minute MNS-on epochs on the rhythmic vs. the arrhythmic day. Subjects who do not complete both stimulation visits will not be included in this analysis. A repeated measures ANOVA will be used to compare effects of visit, order (rhythmic day first or second) and stimulation (on vs. off) on tic frequency. The hypothesized change is a significant interaction of visit, order and stimulation factors ($p \leq .05$),

showing greater improvement (off to on) with rhythmic vs. arrhythmic stimulation. This analysis includes the first six 5-minute blocks on each MNS day (i.e., the blocks that all participants complete).

[Time Frame: During rhythmic MNS stimulation]

4. Change in tic severity during rhythmic MNS (vs. arrhythmic MNS)

   Overall tic severity for each 5-minute block is rated once on a 5-point scale by an expert blind to condition and time point. The scale is the Intensity item from the Yale Global Tic Severity Scale [YGTSS], which uses integer scores from 0 (no tics) to 5 (severe intensity). For this analysis, we will define tic severity as *max*{phonic tic intensity score, motor tic intensity score}. Change in tic severity from baseline (stimulation off) is compared between 5-minute MNS-on epochs on the rhythmic vs. the arrhythmic day. Subjects who do not complete both stimulation visits will not be included in this analysis. A repeated measures ANOVA will be used to compare effects of visit, order (rhythmic day first or second) and stimulation (on vs. off) on tic frequency and severity. The hypothesized change is a significant interaction of visit, order and stimulation factors ($p \leq .05$), showing greater improvement (off to on) with rhythmic vs. arrhythmic stimulation. This analysis includes the first six 5-minute blocks on each MNS day (i.e., the blocks that all participants complete).

   [Time Frame: During rhythmic MNS stimulation]

Secondary Outcome Measures:

5. Change in tic severity after MNS ends

   Duration of benefit will be estimated as follows. A repeated measures ANOVA will compare the change in tic frequency from baseline, during each 1-minute-long period following the end of stimulation. Here baseline means the tic frequency during the last 5 minutes of MNS from the same day.

   [Time Frame: up to 20 minutes after the end of stimulation at each study visit up to 1 month]

6. CGI-I, participant

   Clinical Global Impression of Improvement (CGI-I), rated by participant. The CGI-I is a 7-point scale ranging from 1 = very much improved to 7 = very much worse.

   [Time Frame: 5-25 minutes after the end of stimulation at each study visit up to 1 month]

7. CGI-I, investigator

   Clinical Global Impression of Improvement (CGI-I), rated by investigator.

   [Time Frame: 5-25 minutes after the end of stimulation at each study visit up to 1 month]

8. VAS rating of premonitory urge severity

   Participant rates the maximal severity of any premonitory urges over the preceding minute, from 0=no premonitory urge to 100=maximally uncomfortable premonitory urge, using a Visual Analog Scale.

   [Time Frame: Before MNS begins and at the end of each 5-min. MNS on or off block, at each study visit up to 1 month]

9. Rating of therapeutic effect using the CGI Efficacy Index

   Participant rates peak improvement experienced during the visit using the 4-point scale of the CGI (Unchanged or worse; Minimal - Slight improvement that doesn't decrease the overall impact of

symptoms*; Moderate - Decided improvement. Partial remission of symptoms; Marked - Vast improvement. Complete or nearly complete remission of all symptoms). * = "Minimal" option anchor text slightly edited from original

[Time Frame: 5-25 minutes after the end of stimulation at each study visit up to 1 month]

10. Rating of discomfort using the CGI Efficacy Index (edited)

    Participant rates peak discomfort experienced during the visit using the 4-point scale of the CGI: "Overall, today, how much DISCOMFORT did the stimulation cause? If discomfort is the wrong word, please substitute any negative effects or side effects of stimulation. (No discomfort; Discomfort noticeable, but not severe enough to concern me or to turn it off; Enough discomfort, impairment of functioning or social embarrassment that I would only keep it on if the benefit was considerable; Caused discomfort, impairment of functioning or social embarrassment to a degree that any treatment benefit was not worth leaving it on).

    [Time Frame: 5-25 minutes after the end of stimulation at each study visit up to 1 month]

11. Blindedness assessment

    Participants guess whether they received the active or sham MNS condition, and rate their certainty for that guess on a 0-3 scale (0 = pure guess, 3 = certain).

    [Time Frame: 5-25 minutes after the end of stimulation at each study visit up to 1 month]

12. Interest in a portable stimulator

    Participants answer the question, "If you had a portable device (about the size of a deck of cards) that delivered stimulation in your daily life like you received either today or at your previous visit, would you expect to use it?"

    [Time Frame: Once at the end of the second study visit]

Data analysis

Data storage, sharing and management. Phenotypic data will be collected and stored on REDCap (redcap.wustl.edu). This data will not contain PHI and will be shared on the Open Science Framework. Video recordings will be shared only with explicit optional informed consent.

Overall statistical approach. To prevent "HARKing" (hypothesizing after results are known) [20], we have **registered our hypotheses** and analysis strategy on OSF.io prior to initiating enrollment. For this pilot study, all statistical tests will be reported independently. Aim 1 and Aim 2 test a small number of hypotheses, and Aim 3 results, which are primarily hypothesis-generating, will be presented with a warning about multiplicity of tests.

Aim 1 (replicating the Nottingham results). The analysis will replicate that of Study 3 in the **Current Biology** report [6], with blinded ratings of tic frequency and severity based on the last 40 s of each 60-s MNS on or off block. A one-tailed t test will compare mean tic frequency in on *vs.* off 1-minute stimulation epochs on the rhythmic MNS day. The analysis will be repeated for tic severity.

Aim 2 (testing whether benefit from rhythmic stimulation exceeds that from the active control, arrhythmic stimulation). Change in tic frequency and severity from baseline are compared between MNS-on epochs on rhythmic *vs.* arrhythmic days. Subjects who do not complete both stimulation visits will not be included in this analysis. A repeated measures ANOVA will be used to compare effects of visit, order (rhythmic day first or second) and stimulation (on *vs.* off) on tic frequency and

severity. The hypothesized change is a significant interaction of visit, order and stimulation factors ($p \leq .05$), showing greater improvement (off to on) with rhythmic *vs.* arrhythmic stimulation. The primary analysis will focus on the first six 5-minute blocks (*i.e.*, the ones that all participants complete). A secondary analysis examines the last 40 s of the four 1-minute blocks in the same way. Paired t tests will compare CGI-I ratings between stimulation conditions (rhythmic *vs.* arrhythmic).

Aim 2 interpretation: We chose arrhythmic stimulation as the control condition ("placebo") because it did not increase stimulation-frequency EEG power in the sensorimotor cortex. However, we note that arrhythmic stimulation may itself possibly confer active benefit, which may produce a non-significant result for Aim 2. In that case a different control condition may be required for subsequent study, such as sub-motor-threshold stimulation current or a wait list condition. Additionally, this pilot study will not address the specificity of the stimulation site—as stimulation of another peripheral nerve may prove equally effective—nor the specificity of the 10-12 Hz stimulation frequency. Finally, other modifications may provide greater benefit; *e.g.* bilateral stimulation may be more effective than unilateral. All of these possibilities are reasonable goals of future study, but this pilot study focuses on the methods used in the published work.

Aim 3. The duration of benefit analysis will use a repeated measures ANOVA for tic scores from each 1-minute segment after the end of stimulation. A secondary approach may be to fit the tic scores from each participant after the end of each stimulation block to an exponential decay model. The analysis of individual characteristics that predict improvement with simulation will use a 2-tailed t test or correlation, as appropriate, for each measured demographic and clinical feature. These will include age, sex, baseline YGTSS, baseline OCD severity rating, baseline ADHD severity rating, history of complex tic(s), history of phonic tic(s), and motor and phonic tic frequency and severity at baseline (blinded ratings of the 5-minute block before stimulation on the first study visit). Other outcome variables, such as discomfort, adequacy of blinding, and interest in a portable stimulator, will be summarized descriptively.

Additional analysis details. Outliers will be determined at the level of the individual variables before the main analyses. If the distribution clearly deviates from a normal distribution on visual inspection because of outlying values, after transformation if appropriate, we will use a nonparametric analysis.

SAFETY MONITORING

We anticipate no adverse events other than possible mild, transient discomfort related to the stimulation. However, we will report any adverse events to the Institutional Review Board according to its regulations, including an annual summary.

No serious adverse events (SAEs) are expected. The PI will monitor for unanticipated problems, life-threatening events or deaths. If contrary to expectations any SAE occurs that the investigator considers possibly, probably or definitely related to participation in the study, we will confer with the IRB before continuing enrollment.

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