STUDY IDENTIFICATION

Project title	Open trial of median nerve stimulation for treatment of Tourette syndrome
Short title	Open-label MNS
NCT number	NCT05016765
IRB	Washington University Human Research Protection Office
IRB title	Open trial of median nerve stimulation for treatment of Tourette syndrome
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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.

Among the various questions still to be answered is the question of whether such a device would be practical for use in the real world. In this study, we will supply participants with a commercially available transcutaneous electrical nerve stimulation (TENS) units to use for median nerve stimulation as described in the Nottingham study. Participants will be told to use the device as much or as little as desired to see how such stimulation might be utilized in the real world.

Here we propose (a) to determine the real-world usage and apparent utility of stimulation in people with chronic tics, and (b) to determine momentary self-rated efficacy and side effects of stimulation. In addition, we will compare results from this study to those from the "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot" study, from which participants will be drawn, in order to compare laboratory and real-world efficacy.

Aim 1. Determine the real-world usage and apparent utility of stimulation in people with chronic tics. Participants will be allowed to choose when and for how long to use the stimulation, thus reflecting how patients would use the stimulation in their daily lives outside of a research study.

Aim 2. Determine momentary self-rated efficacy and side effects of stimulation, using surveys taken at the beginning and end of stimulation periods, as well as twice daily when prompted.

Aim 3. Compare results of this trial with those from "Peripheral induction of inhibitory brain

circuits to treat Tourette's: pilot." Participants in this study are drawn from completers of the "peripheral induction" blinded RCT, allowing for clear comparisons between the laboratory conditions of the first study and the real-world conditions of the second.

Completion of these Aims will provide practical information that can inform a future, controlled clinical trial of chronic MNS delivered by a portable 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. All participants will be drawn from completers of the study "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot," and we will draw much of the demographic and clinical information from the RCT. Participants will attend one session (whenever possible, in person at the same visit as the final study visit for the RCT), in which they will learn how to use the device and have it set to appropriate settings. They will then take the device home to use for four weeks, during which time they will fill out brief surveys whenever they turn the device on and off, as well as at two other points throughout the day. These surveys record tic intensity and frequency, as well as discomfort due to the device. Participants will also complete a more extensive survey at the conclusion of the study.

Recruitment

Participants will be recruited from completers of the study "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot."

First visit

1. We present an informed consent document to participants (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 initial visit. Potential subjects will review the informed consent document with the investigator or designee and will have opportunity to resolve questions or concerns. 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. All data from the "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot" study will be imported for comparison with information collected during this study.
3. If more than 2 weeks have elapsed since the most recent administration of the Adult Tic Questionnaire (ATQ) [8,9], participants will be asked to repeat it.

4. Explain use of the TENS unit, including which settings may be changed by the participant and which settings should remain on the settings established by the investigator.

5. Attach electrodes.
6. Determine stimulation threshold (12 Hz, pulse width 200μs), starting at 0 and increasing slowly until a twitch of the thumb is seen.
7. Verify that the participant is able to set up and turn on the device on their own.

Online during study period

1. Participants will complete online measures at the following times:
    a. Turning on the stimulator
        i. Tic intensity
        ii. Tic frequency
    b. Turning off the stimulator
        i. Tic intensity
        ii. Tic frequency
        iii. Discomfort from stimulation
        iv. Overall symptom improvement

    Texts will be sent twice daily at predetermined times, and the participant will respond with times "c." or "d." below depending on stimulator use when the text is received:

    c. Answering a text, stimulator currently on
        i. Tic intensity
        ii. Tic frequency
        iii. Discomfort from stimulation
        iv. Overall symptom improvement
    d. Answering a text, stimulator currently off
        i. Tic intensity
        ii. Tic frequency
2. Participants may be contacted throughout the study for reminders regarding compliance or assistance in troubleshooting issues with the device or surveys.

Online at conclusion of study

1. The study concludes 4 weeks (± 5 days) after the initial visit (or earlier, if the participant decides to stop treatment before 4 weeks).
2. We review the online questionnaires and collect the following additional measures:
    a. Current symptom status
        i. Adult Tic Questionnaire (ATQ) tic rating
        ii. Premonitory Urge for Tics Scale (PUTS) [10]
    b. Treatment efficacy and side effects
        i. Modified Clinical Global Impression – Efficacy Index
        ii. Patient perception of duration of improvement after stimulation
        iii. Patient's plans to continue using device
    c. Open-ended comments
        i. On device
        ii. On study

Subject Payments

Participants will be given the TENS unit to keep at the successful conclusion of the study, a value of approximately $30, to compensate for their loss of time.

Clinical *vs.* research purposes

The actual treatment with MNS is for clinical purposes and will be controlled by the participant. All other 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 may be slightly boring, fatiguing or challenging.

Rare:

- Some participants may be sensitive to components of the electrode pads and develop a rash where the pads are affixed to the skin. If this happens, stop using the device and contact us.
- 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. The exception is that your phone number will be shared with Twilio.com, the text services provider we contract with.

LOCATIONS / SITES OF STUDY

Data collection:	Washington University in St. Louis, and participant's location when answering surveys
Data analysis:	Washington University in St. Louis

STUDY DURATION

Anticipated duration of entire research activity per participant:

- 4 weeks

Anticipated duration of entire research activity:

One year

SAMPLE SIZE

N = 38 (study completers of the "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot" study, which was powered to have 32 study completers with up to 38 participants screened)

Power considerations

As this study is an exploratory study to determine the viability of this type of therapy in the real world setting, the sample size was chosen for convenience to include only completers of the MNS pilot study. However, a sample size of 32 provides 75% power to detect improvement of −25% in tic severity or frequency ratings (one tailed). A change of −25% in YGTSS total tic scores is considered clinically meaningful [17].

INCLUSION CRITERIA

Inclusion criteria for all participants:

- Completed participation in the study called "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot"
- Informed consent by adult participant; assent by child and informed consent by guardian

EXCLUSION CRITERIA

Exclusion criteria for all subjects:

- Has an implanted device that could be affected by electrical current
- Pregnancy known to participant or (for children) to the parent
- Severe or unstable systemic illness
- Factors (such as exaggerated symptom report) that in the judgment of the principal investigator may make the outcome measures inaccurate
- Judged by investigator to be unlikely to complete study procedures

Additional exclusion criteria were required for participation in the RCT.

CONCOMITANT MEDICATIONS

Required: none

PROHIBITED MEDICATIONS

none

TREATMENTS AND DOSAGE

TENS stimulation

- The device (TENS-7000) was judged by the FDA to be substantially equivalent to similar approved devices in the "Transcutaneous electrical nerve stimulator for pain relief" category, 501(k) premarket notification number K080661.
- 12 Hz square-wave, 200 μs pulses will be delivered over the median nerve at the wrist at the threshold for thumb movement to surface electrodes (conductive gel, 30 mm apart center-to-center, anode distal).
- The participant will determine the current delivered, using an analog knob on the TENS unit. We instruct them that we believe the stimulation has to cause thumb movement in order to be effective (based on the Nottingham EEG results), so they will likely need to adjust the current delivered each time they turn it on, given expected fluctuations in actual current delivery with changes in electrode position or electrode-skin resistance throughout the day.
- Participant can choose right or left median nerve (we will suggest their nondominant hand to minimize interference with daily activities).
- Participant will determine duration and timing of stimulation.

ANALYSIS PLAN/APPROACH/METHODOLOGY

Outcome measures

The primary outcome measures are derived from the surveys administered online throughout the study period. Surveys completed when the stimulator is turned on will assess the tic frequency and intensity prior to stimulation. For surveys where the stimulator is currently on or was recently turned off, the tic frequency and intensity will be reported in addition to discomfort and overall symptom relief. The time of each survey will be recorded in order to determine how long the device was on and the relative timing of each survey. Analysis can begin for each participant after their final survey has been completed.

Primary Outcome Measures:

1. Time spent using the device (minutes per day and number of days per week used over four-week period)
2. Do you expect to continue to use the stimulator? (yes/no/maybe, at study conclusion)
3. Comparison of tic frequency between "turning ON" and "turning OFF" surveys (scale of 0-5)
4. Comparison of tic intensity between "turning ON" and "turning OFF" surveys (scale of 0-5)
5. Mean discomfort while using stimulator (scale of 0-3 adapted from the CGI-I Efficacy Index)
6. Relationship to blinded study results (correlation of change in tic frequency and intensity during this study as in outcome measures 3 and 4 above with change in tic frequency and intensity respectively during active, rhythmic stimulation during the RCT).

Secondary Outcome Measures:

1. What was the overall impact of the stimulation on symptoms throughout the study period? (CGI-Efficacy index)
2. How much discomfort did the stimulation cause throughout the study period? (CGI-Efficacy index)
3. Average therapeutic effect while using stimulator
4. Comparison of tic severity prior to and at the end of the study

5. Check whether reported symptom improvement across different stimulation sessions was influenced by stimulation intensity or reported discomfort
6. Comparison of tic frequency between "more than 60 minutes after turning off stimulator" and "less than 60 minutes after turning off stimulator"
7. Comparison of tic intensity between "more than 60 minutes after turning off stimulator" and "less than 60 minutes after turning off stimulator"
8. "How long do you think the improvement in your tics lasted after you turned off the device?"
9. Compare participants' perception of tic improvement from post-study survey to their results collected during the study
10. Compare participants' perception of length of tic improvement after turning off the stimulator from post-study survey to their results collected during the study
11. Do certain participant characteristics predict who will be "responders"?
12. Qualitative analysis of open-ended questions

Data analysis

Data storage, sharing and management. Survey data, which **will not contain PHI**, will be collected and stored on Google Forms. This data will be shared on the Open Science Framework.

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, with a warning about multiplicity of tests. However, we limit the number of primary outcome measures.

Aim 1 (determining real-world utility of stimulation). Descriptive data regarding the duration of use of the device will be reported as the mean and standard deviation of minutes per day, as well as the mean number of days used per participant. Answers to the question, "if you had a free stimulator, would you continue to use it after the study finishes?" will be reported as percentages answering "yes," "no," and "maybe." Additionally, a summary of common themes to the open-ended questions about the device will be reported.

Aim 2 (determining momentary self-rated efficacy and side effects of stimulation). Comparisons of tic frequency and intensity ratings immediately prior to and following use of the simulator will be reported as paired t-tests. A similar analysis will be completed for ratings of frequency and intensity made less than 60 minutes after turning off the stimulator vs. more than 60 minutes after turning off the stimulator (unpaired t tests). Average discomfort and average therapeutic effect while using the stimulator will be reported descriptively as percentage of participants choosing each rating. A similar analysis will be conducted on average discomfort and average therapeutic effect over the entire study period as reported in the final survey. Additionally, the discomfort and therapeutic ratings collected throughout the study will be compared with those taken at the end of the study. Participants' scores on the ATQ (adult tic questionnaire) and PUTS scale (premonitory urge for tic scale) before and after the study will be compared using the paired t-test. Participants' responses to the question "How long do you think the improvement in your tics lasted after you turned off the device?" will be reported as percent of participants choosing each option, and these perceptions will be compared with their numerical ratings throughout the study. Finally, we will determine if certain factors have a significant impact on who is a "responder" to the device, as measured by those participants with a greater than 25% reduction in tic frequency or intensity during stimulation. The factors to be examined include

age, sex, baseline YGTSS, complex tics ever, phonic tics ever, baseline ADHD severity, and baseline OCD severity.

Aim 3 (Compare results of trial with those from "Peripheral induction of inhibitory brain circuits to treat Tourette's: pilot"). Both changes in tic frequency and tic intensity will be compared between the RCT and the open-label study using correlation analysis. The change observed in the RCT will be plotted on the x-axis, and the change observed in the open-label study will be plotted on the y-axis. A line of best fit will be generated to determine if there is a significant relationship between the two, and if so, in what direction it occurs.

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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