Cover page

Official Title of the study: A Randomised, Double-blind, Placebo-controlled, Trial of Rhythmic 10Hz Median Nerve Stimulation for the Suppression of the Urge-to-tic and Reduction of Tics in Individuals With Tourette Syndrome and Chronic Tic Disorder

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Study Protocol with Statistical Analysis Plan

Introduction

Tourette syndrome (TS) and chronic tic disorder (CTD) are neurological conditions of childhood onset that impact approximately 1% of 5-18 year olds (Cohen, Leckman, & Bloch, 2013). Both TS and CTD are characterised by the presence of tics, which are repetitive, purposeless, movements or vocalisations of short duration which can occur many times throughout a day. Tics are highly varied and can range from simple movements and/or vocalisations such as mild eye blinking and throat clearing; to more complex sequences of movement and behaviour, including, mimicking sounds or blurting out obscenities. The majority of adults and adolescents with TS/CTD also experience premonitory urges (PU). PU are uncomfortable sensory phenomena, often described as feelings of discomfort or pressure which can be temporally reduced after tic execution (Cohen et al., 2013). Many individuals with TS/CTD will also experience one or more co-occurring conditions, with the most common being attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) (Freeman et al., 2000).

Tics can have a substantially negative impact on an individual's day-to-day life, with social, occupational/academic, and psychological well-being affected (Conelea et al., 2011; Conelea et al., 2013). Rates of depression are higher in people with TS/CTD than the general population (Robertson, 2006), as is the risk of dying by, or attempting suicide (de la Cruz et al., 2017). Despite these concerning statistics, access to support and treatments for TS/CTD is often limited and sub-optimal.

The two main evidence-based approaches to treating tics are behavioural therapies and medication (Roessner, 2011; Whittington et al., 2016). A recent systematic review found that over half of young people with TS had received medication to help with their tics; however, for many the associated side effects (which can include sedation and weight gain) outweigh the potential benefits (see Hollis et al. (2016) for review). Behavioural treatments such as habit reversal therapy (Azrin & Nunn, 1973) and extensions of this, such as comprehensive behavioural intervention for tics (Piacentini et al., 2010), have been shown to be effective treatments. However, access to specialists who are able to provide this type of therapy is often limited, for example, a UK based study found that approximately 25% of young people with TS had access to behavioural interventions, despite 76% of parents indicating that they would like access to this treatment for their child (Cuenca et al., 2015).

Dysfunction within cortical – striatal – thalamic – cortical (CSTC) circuits has been heavily implicated in the pathophysiology of tic disorders (Greene, Schlaggar, & Black, 2015; Mink, 2006). In particular, it is thought that the dysfunction in CSTC leads to spontaneous firing of the striatum, which releases the thalamus from tonic inhibition, resulting in the increased excitability of the sensorimotor cortex leading to the generation of tics (Worbe et al., 2013; Xu et al., 2015).

In response to the demand for non-pharmacological treatments, numerous studies have utilised non-invasive brain stimulation (NIBS) approaches, with the aim of readdressing imbalances within cortical excitability as a means to reduce tics. The majority of this work has focused on two techniques: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), and targeted primary (M1) and supplementary (SMA) motor regions. Both tDCS and rTMS have been shown to modulate cortical excitability during, and shortly after stimulation, via processes thought to be similar to long term depression (LTD) and long term potentiation (LTP) (Huang, Chen, Rothwell, & Wen, 2007; Nitsche et al., 2003). While some studies have shown significant tic reductions following several sessions of rTMS (Hsu, Wang, & Lin, 2018), the overall picture of results remains somewhat varied, and large scale sham-controlled trials are needed. Furthermore, access to rTMS treatment is typically restricted to research studies, which often involve up to two weeks of consecutive sessions conducted within a clinic/research facility, hence, this approach puts heavy demands on time and resources for both participants and researchers. tDCS is a more portable form of NIBS, and has been trialled in several conditions for home use application (Charvet, Shaw, Bikson, Woods, & Knotkova, 2020); however, relatively few studies of the effectiveness of tDCS on tics have been conducted, and as with rTMS there remains a need for larger scale studies with sufficient control parameters incorporated into the design (Fregni et al., 2020).

A limitation of both tDCS and TMS, is that these approaches both require application of stimulation to the scalp in order to reach the cortical targets below. For optimal targeting of specified brain regions an MRI may be necessary for current flow modelling and optimising coil/electrode placement, this is neither cheap nor easily acquired in groups with movement disorders. Furthermore, the nature of transcranial stimulation is that it is not discrete, and it is unlikely that this technology could be developed into an approach that individuals could use within the home.

An alternative to transcranial stimulation, is to stimulate the peripheral nervous system, which can lead to targeted responses within cortical regions. In recent work using electroencephalography (EEG) we have successfully shown that pulses of electrical stimulation delivered to the median nerve are capable of entraining neural oscillations within the sensorimotor cortex (Morera Maiquez et al., 2020). Houlgreave and colleagues have shown the same effect in healthy adults using magnetoencephalography (MEG) (Houlgreave et al, 2020). Specifically, they demonstrated entrainment of oscillatory activity within the (8-14Hz) alpha band and the (15-30Hz) beta band, which are associated with sensorimotor function (Armstrong, Sale, & Cunnington, 2018). Importantly, it has been shown that when median nerve stimulation (MNS) was administered to people with TS/CTD, their urge-to-tic and the occurrence of their tics substantially reduced (Morera Maiquez et al., 2020). The Morera Maiquez et al. study was conducted with 19 individuals and assessed the immediate impact of MNS applied under experimental conditions. We now build on the encouraging results of this work, by conducting a UK-wide parallel double-blind study in which the potential beneficial effects of numerous sessions of MNS, delivered in the home environment, were evaluated.

Our key aims of the study were as follows:

1. Evaluate the 'online' effects of MNS by exploring alterations in *tic frequency* during MNS, through the use of video recordings collected during the delivery of stimulation.
2. Evaluate the 'offline' or treatment effects of MNS tic severity.

The primary hypotheses are: (a) that active rhythmic MNS will lead to a reduction in tic severity compared to sham stimulation and a waitlist (treatment-as-usual) control group; (b) that active rhythmic MNS will lead to a reduction in tic frequency compared to both sham stimulation; and (c) that rhythmic MNS can be successfully delivered using a wearable 'watch-like' device in a home setting.

Methods

Setting

This trial assessed the effectiveness of 4-weeks of daily, home administered, rhythmic 10 Hz MNS as a treatment for tic disorders. Following an initial baseline assessment/training visit at the University of Nottingham, the trial was conducted within each participant's home, with remote online supervision.

Recruitment

We targeted an enrolment of 135 participants in the trial. Participants were recruited from our existing database of volunteers and through the UK charity *Tourettes Action*.

Inclusion criteria

1. Ages 12 years upward.
2. Confirmed or suspected Tourette syndrome/Chronic tic disorder. With moderate-severe tics, indicated by a total tic score > 15 on the Yale global tic severity scale (YGTSS), or total tic score > 10 if only motor/ vocal tics present.
3. No change in medication for tics or tic-related treatment in the last 2 months. Participants to confirm this during telephone screening.
4. Broadband internet access & electronic device for completion of online materials. For a subset of participants, a device with a camera will also be required.
5. Ability to travel to the University of Nottingham for one onsite visit.
6. Participant is willing and able to give informed consent for participation in the clinical investigation.
7. Able (in the Investigator's opinion) and willing to comply with all clinical investigation requirements.
8. Resident in the UK.

Exclusion criteria

1. Current diagnosis of epilepsy.
2. Participant or participants guardian (if under 16) unable to read/write in English.
3. Participants will be excluded from the trial if they find the stimulation too uncomfortable during the in-person baseline assessment visit.

4. Individuals with implanted electronic devices (e.g. pacemakers, insulin pump, implantable cardioverter defibrillator, neurostimulators)
5. Individuals sharing the household with an individual with implanted electronic devices (e.g. pacemakers, insulin pump, implantable cardioverter defibrillator, neurostimulators)
6. Individuals with a current/recent diagnosis or symptoms of SARS-CoV-2 were not be invited to visit the university until it was safe for them to do so (2 weeks following positive test).
7. Diagnosis of non-verbal autism or similar condition which would affect ability to give informed consent to take part in the study.
8. Pregnant women.
9. Participants who have participated in previous research studies involving median nerve stimulation
10. Participants aged over 90 years old

Initial Screening

Individuals who had indicated an interest in taking part in the study were contacted by a member of the research team to arrange a telephone screening interview. Trial eligibility was then established during this interview using the inclusion & exclusion criteria outlined above. Suitable participants were informed about each step of the trial and the randomisation procedure; they were provided the opportunity to ask questions about the study and received a detailed information sheet. Written informed consent was taken prior to the initial screening videocall and again prior to enrolment in the full trial, if the participant was found to be eligible, using an online form.

Randomization and blinding

Participants were randomly allocated into three groups (ratio: 1:1:1): active rhythmic median nerve stimulation (rMNS) stimulation, sham rMNS stimulation, and a waitlist (i.e., treatment-as-usual and no stimulation). In order to minimize any differences in age, sex and tic severity between groups, a stratified randomisation procedure was followed in which individuals allocated to each group were matched for age, sex and tic severity. The devices used to deliver active and sham stimulation were exactly the same to ensure that researchers were blind to a participant's group allocation. The first 20 participants who were randomly assigned to each group, and who exhibited very frequent tics (i.e. tic-free intervals that were typically no longer than 5min), were selected as a subgroup who were required to additionally provide video recordings immediately prior to, during, and immediately after they received stimulation. These recordings were used to assess online effects of rMNS stimulation.

Importantly, the member of the research team allocating participants to each condition was not involved in either the collection or processing of measurement outcomes (questionnaire/ video data). Similarly, the researchers responsible for programming the wearable MNS devices, to deliver either sham/active stimulation, were not involved in the collection or processing of measurement outcomes (questionnaire/video data). All other members of the research team, participants, and legal guardians were entirely blind to sham/active group allocation. Participants allocated to the waitlist group were not blind to the type of stimulation they would go on to receive at the conclusion of the trial (i.e., all participants initially allocated to the waitlist group went on to receive active rMNS at the conclusion of the trial).

Baseline data collection and visit

Prior to any further measures being collected, a subset of 16 participants from each group were asked to video record themselves during restful activity (such as watching television) for 5 minutes on 5 consecutive days. The purpose of this was to obtain a baseline of tics for these individuals prior to any intervention. Participants were instructed how to video record themselves, and how share the video with the research team, through a videocall training session.

All participants allocated to the active and sham groups were then invited to the University of Nottingham. During this visit, the participants received their stimulation device and were trained on its correct placement and use. In order to ensure participant's comfort with the stimulation, a practice session was performed. If the participant experienced significant discomfort, they were withdrawn from the trial. On the same day, demographic information along with primary and secondary measures were collected using various questionnaires and structured interviews. Participants in the waitlist group also completed these measurements online and through a video call.

Participants in the active and sham stimulation groups returned home with the device and were instructed to commence stimulation sessions on a Monday within 3 weeks of their visit.

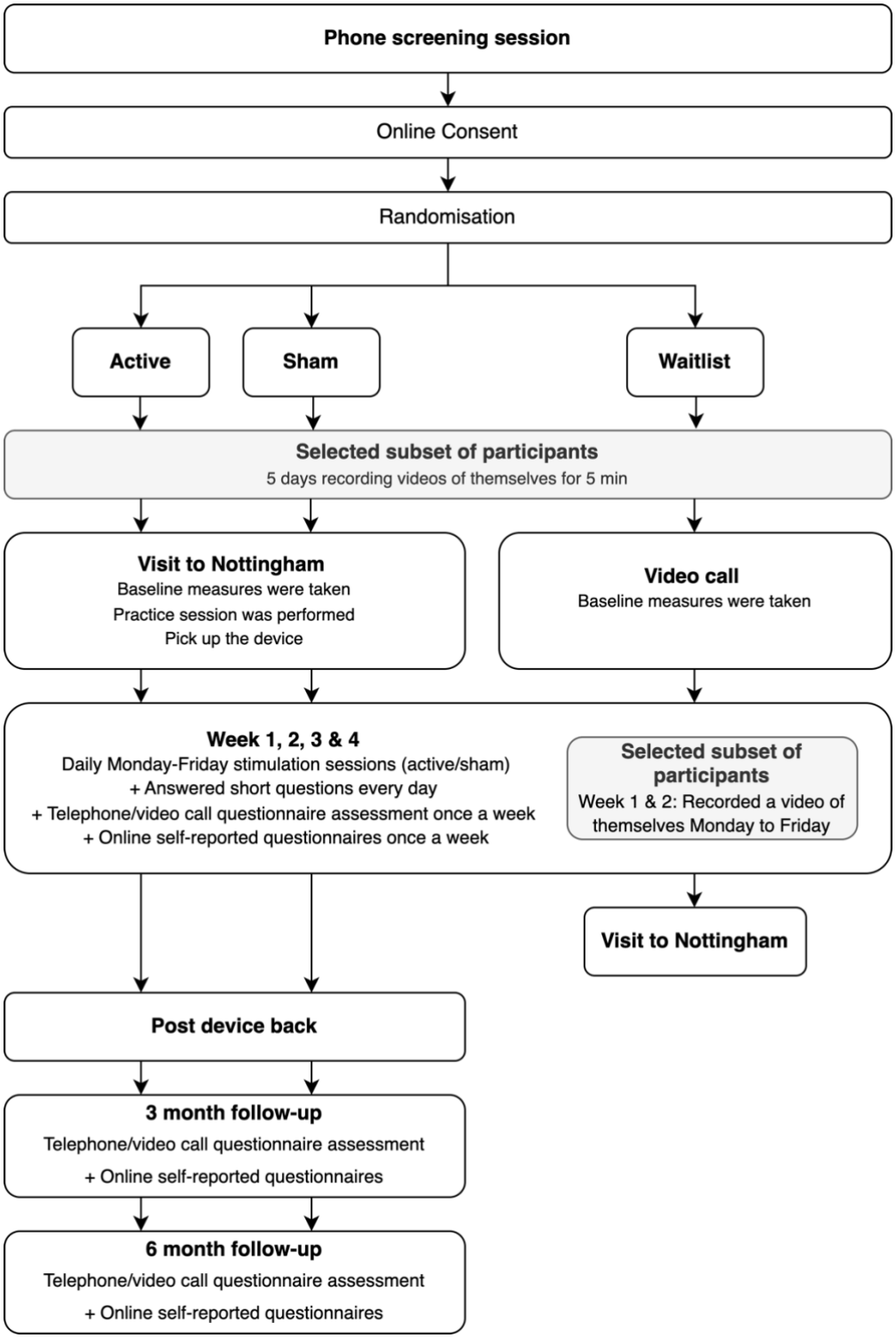
Trial design

A randomised, parallel, double-blind, sham-controlled design was used for this trial (active stimulation vs. sham stimulation condition). The trial also included an open label, waitlist (treatment-as-usual) control condition, in which participants experienced treatment as usual prior to receiving active stimulation at the conclusion of the trial. After screening and attending a baseline visit at the University of Nottingham the active and sham groups were asked to use the stimulation daily from Monday to Friday, within their own homes for 4 consecutive weeks. The waitlist group did not receive stimulation for the first four weeks, but were then provided with devices set for active stimulation for home administration (i.e., similar to that provided for the active stimulation group). However, unlike the active stimulation group, the participants in the waitlist group were not blind to the stimulation type they would receive. Outcome measurements based upon questionnaires and semi-structured interviews were obtained at baseline, and weekly during the 4 weeks of stimulation, and then at 3-month and 6-month follow-up (see schematic in Figure 1). Parents of participants under 18 years old were asked to be present during the online and video call measures, and while the participant used the stimulation device.

As noted previously, a subset of 16 participants from each group were asked to record short video recordings of their tics. Initially this involved recording for 5 minutes on 5 consecutive days to create a baseline measure of tic severity. Then, during the first two weeks of stimulation use, the subset of participants in the active and sham stimulation groups were asked to video record themselves immediately before stimulation (5 mins), during stimulation (14 mins) and immediately after stimulation (5 mins). The subset of 16 participants on the waitlist group were asked to record 5 minute videos of themselves over the same time period. Video recording took place on weekdays (Monday-Friday) at approximately the same time of day. Participants were requested to collect these video recordings while sitting at a table and engaged in a passive, restful, activity such as watching television.

After 4 weeks of device use, participants were asked to return the device. Questionnaires and semi-structured interviews to assess primary and secondary outcome measures were repeated at 3 and 6 months after the start of the stimulation sessions. At the end of the trial, participants were fully debriefed and informed into which group they had been allocated. Here we are reporting data collected at baseline and during the 4-week stimulation phase of the trial. Data for the 3-month and 6-month follow-up will be reported separately at a later point in a further publication.

A schematic flow diagram of the trial design is shown in *Figure 1*.



Delivery and monitoring of MNS

We used wearable stimulation devices specially designed and built for this trial, with the aim of delivering rMNS stimulation in a similar manner to that reported in a previous study (Morera et al., 2020). These devices were lightweight, wireless and easy to operate. Importantly, participants were not able to edit the device parameters once these had been

programmed, thus the duration, frequency and intensity of stimulation remained fixed throughout the trial for each participant. To ensure that all participants underwent daily sessions of stimulation, the device incorporated software that updated the research team after each use. The device was also restricted so that it could only be used once each day. To ensure that the participants were wearing the device during stimulation, the device only operated if it was correctly attached to the wrist.

The intensity of stimulation (1-19 mA) was individualised for each participant based on the approach previously used in Morera et al. (2020). Specifically, we defined the stimulation threshold for each participant by delivering single pulses to the wrist at an increasing intensity until a visible contraction in the thenar muscle was observed. Note, as MNS can be painful at high stimulation intensities, and as we were working with young children, it was not feasible to find individual thresholds using a descending staircase procedure. Instead, we used an ascending staircase to find an initial estimate of the minimum stimulation intensity required to produce a twitch of the thenar muscle and then made small adjustments to stimulation intensity, both up and down, until we were satisfied we had found a reliable estimate of 'threshold'. The mean stimulation intensity (i.e., 120% of threshold) for the entire sample was 10.7 ± 3.6 mA (95% CI: 5.1 – 17.2 mA).

In the active group, a session of stimulation consisted of delivering rhythmic pulse trains of MNS at a frequency of 10Hz in which each pulse was of 200 μs (i.e., 0.2 ms) duration and was delivered at 120% of motor threshold, in bursts of 2 minutes of stimulation followed by 1 minute of no stimulation. This was repeated 5 times, lasting 14 minutes in total. Stimulation was delivered on the wrist of their right hand. In the sham group, the same pattern and total duration of stimulation was applied; however, for the first 15 seconds of each session only, stimulation was delivered at 120% motor threshold, after which it was ramped down to 50% of motor threshold thereafter. This approach to sham stimulation ensured participants initially felt the stimulation prior to it being reduced. Pilot data using magnetoencephalography (MEG) demonstrated that MNS delivered at 50% of stimulation threshold does not cause entrainment of neural oscillations.

Sample size

Based on previous studies (e.g. Debes et al. (2015); Jankovic et al. (2016); Morera Maiquez et al. (2020); Stenner, Baumgaertel, Heinze, Ganos, and Muller-Vahl (2018)) we estimated that a 6-point reduction (i.e., 25% reduction) in the YGTSS total tic severity score (YGTSS-TTSS) would indicate a clinically meaningful improvement in tic severity (Jeon et al., 2013). Since we predicted that there would be a clinical improvement in the active group compared to the sham and waitlist groups, a one-sided type I error of 2.5% with a 90% power required a total sample of 39 participants per group. Furthermore, in order to allow for a 13% dropout, 45 participants per group, and a total of 135 participants, were recruited for the trial. The sample

size for the study exploring the online effects of the stimulation using video data was established as 16 participants per group. This was treated as exploratory analyses.

Measures

A combination of self-report questionnaires, semi-structured interviews, and video recording of tic frequency were used. These were collected during the baseline in-person visit, through online forms or through video/telephone calls. All interview-based measures were completed by trained researchers. Where possible, the same researcher assessed the same participant throughout the trial. Video/telephone calls were recorded for quality checks. Any changes in tic medication/treatment during the trial were noted. A schematic flow diagram of the trial measures is shown in Supplementary Figure 1.

Demographic measures

To assess characteristics of the participant sample, the following measures were taken during the baseline assessment. These measures were collected in person for the sham and active groups during their visit to the University of Nottingham. Measures were collected using video call and through online forms for those in the waitlist group, with the exception of the IQ measure which was collected in-person when participants visited the university to start the open label active phase of the study.

- The Autism-spectrum quotient [AQ]/autism-spectrum quotient adolescent (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001): 50-item self-report measure giving an indication of autistic traits.
- Edinburgh Handedness Inventory–short form [EHI] (Veale et al, 2014): 4-item self-report measure to assess hand dominance.
- Wechsler's abbreviated scale of intelligence, two subtests form (WASI-II). (Wechsler, 2011): researcher lead assessment of matrix reasoning and vocabulary used to provide a rough IQ estimate.
- Becks depression inventory (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961): 21-item self-report questionnaire to assess symptoms of depression.
- Age appropriate measures were used to assess symptoms of ADHD: the World health organisation adults ADHD self-report scale (ASRS) (Kessler et al., 2005) or Conners comprehensive behavioural ratings scale self-report (Conners, 2008); dependant on the age of participant.
- Estimated age of tic onset.
- Any previous treatments received to help with tics.
- Any confirmed current diagnoses of co-occurring neuropsychiatric conditions.
- Current prescribed medications for tic disorders and/or co-occurring neuropsychiatric conditions.

Primary outcome measures

The primary outcome measure was the Yale Global Tic Severity Scale revised [YGTSS-R] total tic severity score [TTSS] (McGuire et al. 2018). The YGTSS is a validated, researcher-administered, semi-structured symptom checklist of 46 tic disorder symptoms occurring

within the last week. The YGTSS-TTSS includes subscales for tic number, frequency, intensity, complexity and interference. These subscales can be combined to form total motor tic score and total phonic tic score, each with a possible rating of 0-25. By combining the two scores the total tic severity score is calculated. The YGTSS was administered by a trained researcher blind to the experimental group of each participant. The first YGTSS measure was conducted in person (sham/active stimulation groups) or through video call (open label waitlist group). Subsequent measures of the YGTSS were completed by video call at weeks 1-4, at 3 months follow-up and 6 months follow-up.

Secondary outcome measures

Secondary outcome measures were taken at various time points, including at baseline, weeks 1-4, and at 3 and 6 month follow-up.

- Premonitory Urge for Tics Scale-Revised [PUTS-R] (Baumung et al., 2020): The PUTS-R is a 24 item self-report instrument which is specifically designed to measure the current frequency of different types of premonitory urges in patients with tic disorders. We used the total score on PUTS-R as a primary outcome measure to assess changes in premonitory urge.
- (Children's) Yale-Brown Obsessive-Compulsive Scale (C)Y-BOCS (Goodman et al., 1989; Scahill et al., 1997): The age appropriate version of this semi-structured interview was used to assess symptoms of OCD. The first part of the scale involves assessing what potential obsessions/compulsions an individual has experienced over the course of the past week, followed by assessment of the time spent, interference and distress caused by, ability to resist, and control over obsessions/compulsions.
- Gilles de la Tourette Syndrome – Quality of Life scale (TS-QoL) (Cavanna et al., 2013; Cavanna et al., 2008): The age appropriate version of this 27-item semi-structured interview consisting of four subscales (psychological, physical, obsessive-compulsive and cognitive) which can be combined to give a single measure indicating overall quality of life was used. The questionnaire also includes a measure of current satisfaction with life using a visual analogue scale (VAS).
- Becks anxiety scale (BAS) (Beck, Epstein, Brown, & Steer, 1988) 21-item self-report questionnaire to assess symptoms of anxiety.
- Yale Global Tic Severity Scale revised [YGTSS-R] impairment score (McGuire et al. 2018). The impairment score is a value of 0-50 given by participants in response to a question about the level of distress and impairment they feel as a result of their tics in areas of daily life including interpersonal, academic and occupational.

Note, data from all measures collected at 3-month and 6-month follow-up will be reported separately at a later time.

Video recording of tics

A subset of participants were asked to record videos of themselves, and share these daily with the research team. The videos included the participant's face and upper body, but did not include the hand being stimulated at rest. Each video was reviewed daily for quality by a member of the research team who was not involved in either the collection or processing of measurement outcomes (questionnaire/ video data), to ensure it met the following criteria:

- The room is well-lit and the participant's face and facial tics can be clearly seen.
- The participant is sitting at a table with their recording device in front of them.
- The participant's face and upper body are in the video.

- The participant's hands are not in the video.
- The participant's whole face is visible throughout the entire recording.
- The participant is quiet and not speaking or singing during the recording.
- The room is in silence during the recording, making vocal tics easy to hear.
- The participant is relaxed and is not engaging in activities involving voluntary movements, such as such as using their phone.
- The participant has recorded approximately 5 minutes before starting the device and continues to record for approximately 5 minutes after the end of the stimulation.

Statistical analyses and data processing

Our preference is to report effect sizes and to use non-parametric permutation statistics and/or Bayesian hypothesis testing where appropriate to circumvent issues associated with changes in sample size (i.e., drop-out or missing data) or sample variance (to be expected if the intervention is effective for some but not all participants). Statistical analysis using parametric analyses (e.g., ANOVA) are also used where this is appropriate.

Demographic information:

Demographic data are summarized by group. Continuous data within groups is reported as mean and standard deviation (SD), median and inter-quartile range (IQR). Categorical data within groups is reported as a percentage.

Primary outcome analyses: Change in tics indicated by YGTSS-TTTS, YGTSS-motor and YGTSS-phonic scores

To assess the effect of 4 weeks of daily rMNS treatment on tic severity, we calculated individual difference scores for each measurement by subtracting each individual's YGTSS score measured at baseline from their score measured at the end of the 4-week stimulation period (i.e. week 4). Then, to assess between-group differences in reduction in tic severity, we conducted planned contrasts (i.e., active vs. sham; active vs. waitlist, and sham vs. waitlist) of the mean difference measurements using non-parametric permutation testing.

Secondary outcome analyses:

Individual difference scores were computed (as above) for secondary outcome measures, specifically: YGTSS-impairment score; premonitory urge (PUTS-R) score; and OCD symptoms (CY-BOCS). Between-group differences are assessed as outlined above.

Exploratory analyses:

Multiple regression analyses were used to explore potential predictive relationships between change in tic severity (measured at week 4) and measures of co-occurring conditions/symptoms measured at baseline. Specifically, the variables: group membership, OCD total score (CY-BOCS-total), OCD obsessions score (CY-BOCS-obsessions), OCD compulsions score (CY-BOCS-compulsion), and standardised ADHD score (standardised ASRS or Conners scores) were used to predict change in YGTSS-TTSS at week 4.

Video data analyses:

As analysis of video data is extremely time consuming, we reduced the video data prior to statistical analysis as follows. For each week, 3 of a possible 5 daily recordings were selected

at random for analysis. A video start time was randomly generated, and a 1min 50s video segment from commencing at this time point was selected for detail analysis. The same time points were assessed for each of the video sessions selected for that week. Videos collected during the 5 day baseline, and all videos collected from the waitlist group, were 5 minutes long and were processed as above. Videos collected during stimulation from the active and sham stimulation groups consisted of 5 minutes video recorded immediately prior to stimulation, 14 minutes of video recorded during while stimulation was delivered, and 5 minutes of video recorded after stimulation had ceased. For these videos, 1min 50s segments from each of these three time periods were randomly selected for assessment. Note, for clarification, in all cases in which a 1min 50s segment was selected from the 14 minute 'stimulation' period, this segment always contained 1min 50s during which stimulation was delivered, and commenced 10s after the start of the selected 2 minute period of stimulation.

This data reduction approach generated 5 minutes and 30 seconds of baseline video for each participant regardless of group. From the subsequent two-week period of recording, data reduction ideally resulted in 11 minutes of video for each participant in the waitlist group and 33 minutes for each participant in the sham and active groups. For each participant in the active and sham stimulation groups, the 33 minutes of video data would consist of 11 minutes prior to, 11 minutes during and 11 minutes after stimulation. The number of tics per minute (TPM) were calculated for each video recording session and the '*online'* effects of stimulation was assessed by calculating, for each session, the difference in TPM measured during stimulation from that measured immediately prior to stimulation. In this way, the online effects of stimulation were always referenced to current levels of tic frequency.

Tic counting (coding) was conducted by highly experienced researchers. The individuals who coded video recording sessions assessed 1.5 times the minimum number of participant videos per group x3 to create overlap between codes and permit assessment of coder reliability. Video assessment was performed by noting the time of every tic, together with information about what part of the body or type of vocalisation was involved. Importantly, coders were blind to the group membership of the participant, when the video was collected, and whether the video segment was from the period prior to stimulation, during stimulation, or post stimulation. Specifically, videos segments were provided to coders with a randomly generated name that did not contain any information about when the video was collected. The 1min 50s segments selected from each video session were randomised to create a video in which coders did not know whether the participant had already received stimulation, was receiving stimulation or had not yet received stimulation. Where possible, coders counted videos from participants they had been assessed during baseline, as they were familiar with that participant's tics. Coder reliability was accepted at 80% agreement or greater, for each 1min 50s section of each video. If two coders had an agreement below 80% in any of the 1min 50s sections of a video, the two coders met and went through the video together until an agreement of +80% was reached. If +80% agreement was still not met, a third highly experienced researcher met with the coders and went through the video together until an agreement of +80% was reached. Once reliability had been achieved, an average of the tic counts was calculated for each section of each participant's video. To increase reliability success, a highly experienced researcher met with the coders weekly to go through video sections in which movements and/or vocalisations were difficult to determine whether they were tics or voluntary actions.

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