A 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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Keywords:

Tourette syndrome; Tics; median nerve stimulation; placebo-controlled trial;

Acknowledgements

This work was supported by Tourettes Action (UK) and the NIHR Nottingham Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. We thank Tourettes Action (UK) for assisting with participant recruitment.

Data Availability

The data that support the findings of this study will be available on request from the corresponding author, [SRJ]. The data are not publicly available due to ethical restrictions and their containing information that could compromise the privacy of research participants.

Abstract

Tourette syndrome (TS) and chronic tic disorder (CTD) are neurodevelopmental disorders that are characterised by the occurrence of tics; repetitive, purposeless, movements or vocalisations of short duration which can occur many times throughout a day. One of the defining characteristics of tics, and one that distinguishes them from other kinds of abnormal movement, is that they can often be suppressed for a period of time. However, tic suppression is invariably associated with increasing levels of discomfort which is most often experienced as a strong urge-to-tic (PU). Importantly, PU are uncomfortable sensory phenomena, often described as feelings of discomfort or pressure which can be temporally reduced after tic execution. Individuals who experience PU often report that: these experiences are more *bothersome* than their tics; that expressing their tics give them *relief from*, and temporarily *abolishes*, their PU; and that *they would not exhibit tics if they did not experience PU*. For this reason, PU might be considered as the driving force behind the occurrence of tics. Currently effective treatment for TS is an area of considerable unmet clinical need. Furthermore, when individuals with TS are asked to comment on research priorities for TS, they frequently state that developing a low-cost, safe and effective, non-drug treatment for controlling tics and the urge-to-tic, that would be suitable for administration outside of the clinic, should be of the highest priority. We propose to conduct a parallel, double-blind, placebo-controlled trial of a wearable, wrist-worn, therapeutic device for the suppression of PU and the reduction of tics in individuals with TS. The device is programmed to deliver rhythmic (10Hz) trains of low-intensity (1-19 mA) electrical stimulation to the median nerve for a pre-determined duration each day, and will be used by each participant from home once each day, 5 days each week, for a period of 4 weeks. A total of 135 participants (45 per group) will be randomly allocated to an; active stimulation; sham stimulation; or waitlist (i.e., treatment as usual) group using Randola (http://rando.la/). Recruited participants will be individuals with confirmed or suspected Tourette syndrome/Chronic tic disorder aged 12 years upward with moderate to severe tics. Participants with epilepsy will be excluded. Researchers involved in the collection or processing of measurement outcomes and assessing the outcomes, as well as participants in the active and sham groups and their legal guardians will be blinded to the group allocation.

Primary measurements of the effects of stimulation will focus on standard clinical measures of tic severity and the urge-to-tic. Additional analyses will evaluate changes in quality-of-life and symptoms linked to frequency of co-occurring clinical conditions. Follow-up assessments will take place at 3 months and 6 months after the trial commenced. The primary hypothesis is that active rhythmic MNS will lead to a reduction in tic severity compared to sham stimulation.

Introduction

Tourette syndrome (TS) and chronic tic disorder (CTD) are neurodevelopmental disorders that are found in the majority of cultures worldwide (Robertson, Eapen, & Cavanna, 2009) and 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). Importantly, individuals who

experience PU often report that: these experiences are more *bothersome* than their tics; that expressing their tics give them *relief from*, and temporarily *abolishes*, their PU; and that *they would not exhibit tics if they did not experience PU* (Cavanna, Black, Hallett, Voon, 2017). Awareness of PU typically increases with age, with the delayed reporting of this experience thought to be resultant of development in self-awareness (Leckman, Walker, & Cohen, 1993). 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 outside of the home.

An alternative to transcranial stimulation, is to stimulate the peripheral nervous, 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). We have also shown the same effect in healthy adults using magnetoencephalography (MEG) (Houlgreave et al, 2020). Specifically, we were able to show entrainment of oscillatory activity within the (8-14Hz) alpha/mu band and the (15-30Hz) beta band, which are associated with sensorimotor function (Armstrong, Sale, & Cunnington, 2018). Importantly, we also found 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). Our original study was conducted with 19 individuals and assessed the immediate impact of MNS applied under experimental conditions. We now wish to build on the encouraging results of this work, by conducting a large-scale double-blind study in which the potential beneficial effects of numerous sessions of MNS, delivered in the home environment, will be evaluated.

Our key aims of the study are as follows:

1. Evaluate treatment effects of MNS on the occurrence of tics and the urge-to-tic.

2. Evaluate treatment effects of MNS on impairment and well-being.

2. Evaluate the effects of MNS on co-occurring OCD symptoms.

3. Evaluate the long-term effects of MNS.

4. Explore the changes in tic frequency occurring during and immediately following MNS, through the use of video data in a subgroup of participants.

The primary hypothesis is that active rhythmic MNS will lead to a reduction in tic severity compared to sham stimulation. To examine any placebo effect, we will compare the measures of tic severity between the sham stimulation and no stimulation groups, and we predict that tic severity will be reduced in the sham stimulation group. Our secondary hypothesis is that MNS will also have a positive beneficial effect on urges, impairment, well-being and co-occurring OCD symptoms compared to both sham stimulation and no stimulation.

Methods

Setting

This trial aims to assess the effectiveness of home use of rhythmic mu-band MNS as a treatment for tics. The trial will be conducted from participant's homes, with remote supervision, following an initial baseline assessment visit occurring at the University of Nottingham.

Recruitment

135 participants will be enrolled in the trial. Participants will be recruited from our database 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.

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.

Initial screening

Participants who indicate an interest in taking part in the study will be contacted by a member of the research team who will arrange a telephone screening interview. Trial eligibility will be established during this interview using the inclusion & exclusion criteria. Suitable participants will be informed about each step of the trial and the randomisation procedure; they will have the opportunity to ask questions about the study and receive a detailed information sheet. Informed consent to take part in the trial will be obtained using an online form prior to randomization.

Randomisation and blinding

Participants will be randomly allocated into three groups (ratio: 1:1:1): active stimulation, sham stimulation and waitlist (no stimulation). In order to minimise the difference in age, gender and severity between groups, we will perform a stratified randomisation for age, gender and severity (using YGTSS Total Tic Severity Score) using *Randola* (http://rando.la/) to allocate individuals to each group. The devices used to deliver active and sham stimulation will be exactly the same to ensure allocation concealment of researchers. The first 20 participants randomly assigned to each group, who have very frequent tics (i.e. tic-free intervals that are typically no longer than 5min), will be selected as a subgroup to additionally provide the video recording measurements needed to assess online effects of stimulation.

Importantly, the member of the research team performing allocation will not be involved in the collection or processing of measurement outcomes (questionnaire/ video data). This same researcher will also be responsible for assigning participants to interventions by programming the MNS devices to deliver sham/active stimulation. All other members of the research team, participants and legal guardians will be blind to sham/active group allocation. Participants allocated to the waitlist group

will not be blind to the stimulation type they will receive (i.e., all participants initially allocated to the waitlist group will go on to receive active rhythmic MNS at the conclusion of the trial).

Baseline data collection and visit

Prior to any further measures, a subset of 20 participants from each group will be asked to video record themselves during restful activity (such as watching television) for 5 minutes on 5 consecutive days. The purpose of this is to obtain a baseline of tics for these individuals prior to any intervention.

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

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

Trial design

A randomised, parallel, double-blind, sham-controlled design will be used for this trial (active stimulation vs. sham stimulation condition). The trial will also include an open label, waitlist condition, in which participants will experience treatment as normal prior to receiving active stimulation at the conclusion of the trial period. After screening and attending a baseline visit at the University of Nottingham, the active and sham groups will be asked to use the stimulation daily from Monday to Friday, within their own homes for 4 consecutive weeks. The waitlist group will not receive stimulation for the first four weeks, but will then be 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 will not be blind to the stimulation type they will receive. This will provide a further useful comparison (i.e., between blind and open label active stimulation) to evaluate directly the effects of active MNS stimulation. All participants will complete weekly questionnaires and semi-structured interviews to assess changes in tics, urges, well-being, anxiety and OCD symptoms at various timepoints throughout the trial (see schematic in Figure 1). Parents of participants under 18 years old will be asked to be present during the online and video call measures, and while the participant uses the stimulation device.

As noted previously, a subset of 20 participants from each group will be asked to record short video recordings of their tics. Initially this will involve 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 will be asked to record video of themselves immediately before stimulation (5 mins), during stimulation (14 mins) and immediately after stimulation (5 mins). The subset of 20 participants on the waitlist group will be asked to record 5 minute videos of themselves over the same time period. Video recording should take place on weekdays (Monday-Friday) at approximately the same time of day. Participants will be 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 will be asked to return the device. Questionnaires and semi-structured interviews to assess changes in tics, urges, well-being, anxiety and OCD symptoms will be subsequently repeated at 3 and 6 months after the start of the stimulation sessions. At the end of the trial, participants will be fully debriefed and informed into which group they had been allocated.

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

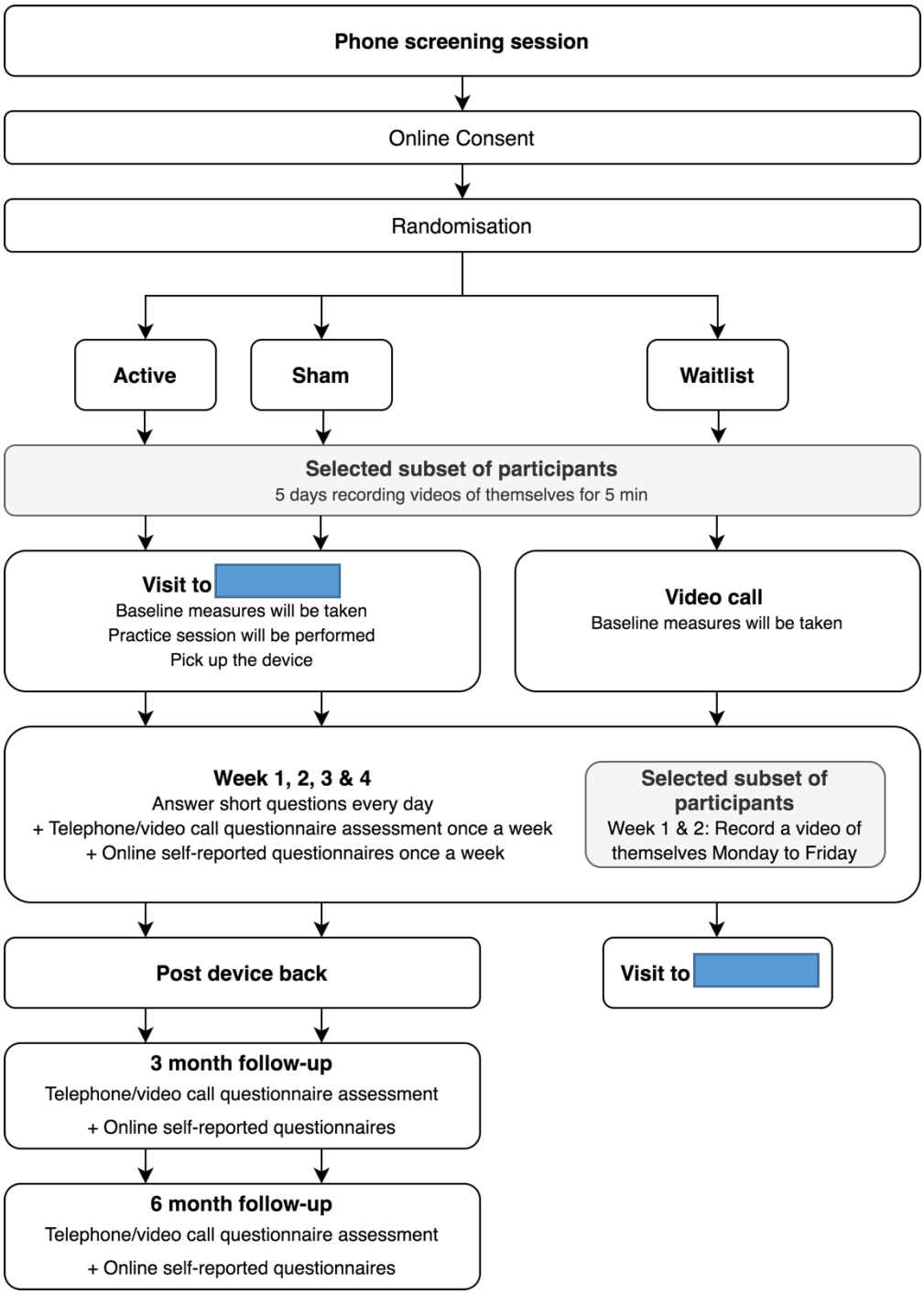

Figure 1. Schematic flow diagram of the trial design

Delivery and monitoring of MNS

We will use wearable stimulation devices specially designed and built for this trial, with the aim of delivering stimulation in a similar manner to a previous study (Morera et. al, 2020). These devices will be wireless and easy to use. Importantly, participants will not be able to edit the device parameters once these have been programmed, therefore the duration, frequency and intensity of stimulation will remain fixed throughout the trial for each participant. To ensure that all participants are undergoing daily sessions of stimulation, the device will incorporate software that will update the research team after each use. The device will also be restricted so that it can only be used once a day.

To ensure that the participants are wearing the device during stimulation, the device will only switch on once it is attached to the wrist. Data from participants skipping 25% or more of the sessions will be excluded from analysis.

The intensity of the stimulation (1-19 mA) will be individualised for each participant based on the approach previously used in Morera et al (2020). Specifically, the motor threshold for the participant will be determined by delivering single pulses to the wrist at an increasing intensity until a contraction in the thenar muscle is seen. In the active group, a session of stimulation will consist of delivering rhythmic pulse trains of MNS at a frequency of 10Hz in which each pulse of 200 μs (i.e., 0.2 ms) duration is delivered at 120% of motor threshold, in bursts of 2 minutes of stimulation followed by 1 minute of no stimulation. This will be repeated 5 times, lasting 14 minutes in total. Stimulation will be delivered on the wrist of the dominant hand. In the sham group, the same pattern and total duration of stimulation will be applied; however, for the first 15 seconds of each session only, stimulation will be delivered at 120% motor threshold, after which it will be reduced to 50% of motor threshold. This approach to sham stimulation should ensure participants initially feel the stimulation prior to it being reduced. Pilot data has demonstrated that MNS delivered below motor threshold does not cause entrainment of neural oscillations.

Sample size

We assume that an average 6-point reduction (i.e., 25% reduction) in the YGTSS total tic severity score (YGTSS-TTS) would indicate a meaningful clinical improvement in tic severity (Jeon et al., 2013). 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)), the standard deviation (SD) in YGTSS-TTS is typically below 9. Since we predict that there will 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 requires 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, will be recruited for the trial. The sample size for the study exploring the online effects of the stimulation using video data will be 20 participants per group. This will be treated as exploratory analyses, and we are aware that the analyses performed on this data may have lower statistical power, however it is nonetheless larger than a previous study that demonstrated robust and statistically significant effects of online MNS on tic frequency in TS (Morera Maiquez et al., 2020).

Measures

A combination of self-report questionnaires, semi-structured interviews and video recording of tics will be used. These will be collected during the baseline in-person visit, through online forms or through video /telephone calls. All interview-based measures will be completed by trained researchers. When possible, the same researcher will assess the same participant throughout the trial. Video/telephone calls will be recorded for quality checks. Any changes in tic medication/treatment during the trial will be noted. A schematic flow diagram of the trial measures is shown in *Figure 2.*

Demographic measures

To assess characteristics of the participant sample, the following measures will be taken during the initial baseline. These measures will be collected in person for the sham and active groups during their visit to the University of Nottingham. Measures will be collected using video call and through online forms for those in the waitlist, with the exception of the IQ measure which will be collected in-person when participants visit 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.
- 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 age of participant. Age appropriate version will be used to assess symptoms of ADHD.
- Estimated age of tic onset.
- Any previous treatments received to help with tics.

Primary outcome measures

- Yale Global Tic Severity Scale revised [YGTSS-R] total tic severity score (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 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 will be administered by a trained researcher who is blind to the experimental group of each participant. The first YGTSS measure will be conducted in person (sham/active stimulation groups) or through video call (open label waitlist group). Subsequent measures of the YGTSS will be completed over video call at week 1, week 2, week 3, week 4, and at 3 months and 6 months after starting stimulation. Whenever possible the researcher conducting the interviews will remain constant for each participant. With the participant's permission, interviews will be recorded for quality control.

Secondary outcome measures

Secondary outcome measures will be taken at various time points including at baseline week 1, 2, 3 and 4, and at follow-up points 3 and 6 months after starting stimulation; except for Gilles de la Tourette Syndrome – Quality of Life scale and the Becks anxiety scale, which will be taken at

baseline, week 4 and at follow-up points 3 and 6 months after starting stimulation. See schematic (Figure 2) for planned time course of each measure. Initial baseline measures will be completed in person for those in the sham/active groups and through video call for those in the waitlist group.

- 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 will use 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 will be 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 will be 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.

- During the initial 4 weeks of the trial, participants will be asked to answer the following questions using a Likert scale of 1-5.
    - How were your tics today?
    - How were your urges to tic today?
    - How comfortable did you find today's stimulation?

Other measures

- During each video call at weeks 1, 2, 3 and 4, and during the 3 months and 6 months follow up participants will be asked if there has been any change to their medication or if they have enrolled in any other tic based treatments.

- Video data: A subset of participants will be asked to record videos of themselves. The videos will include the face and upper body of the participant and will not include the hand being stimulated.

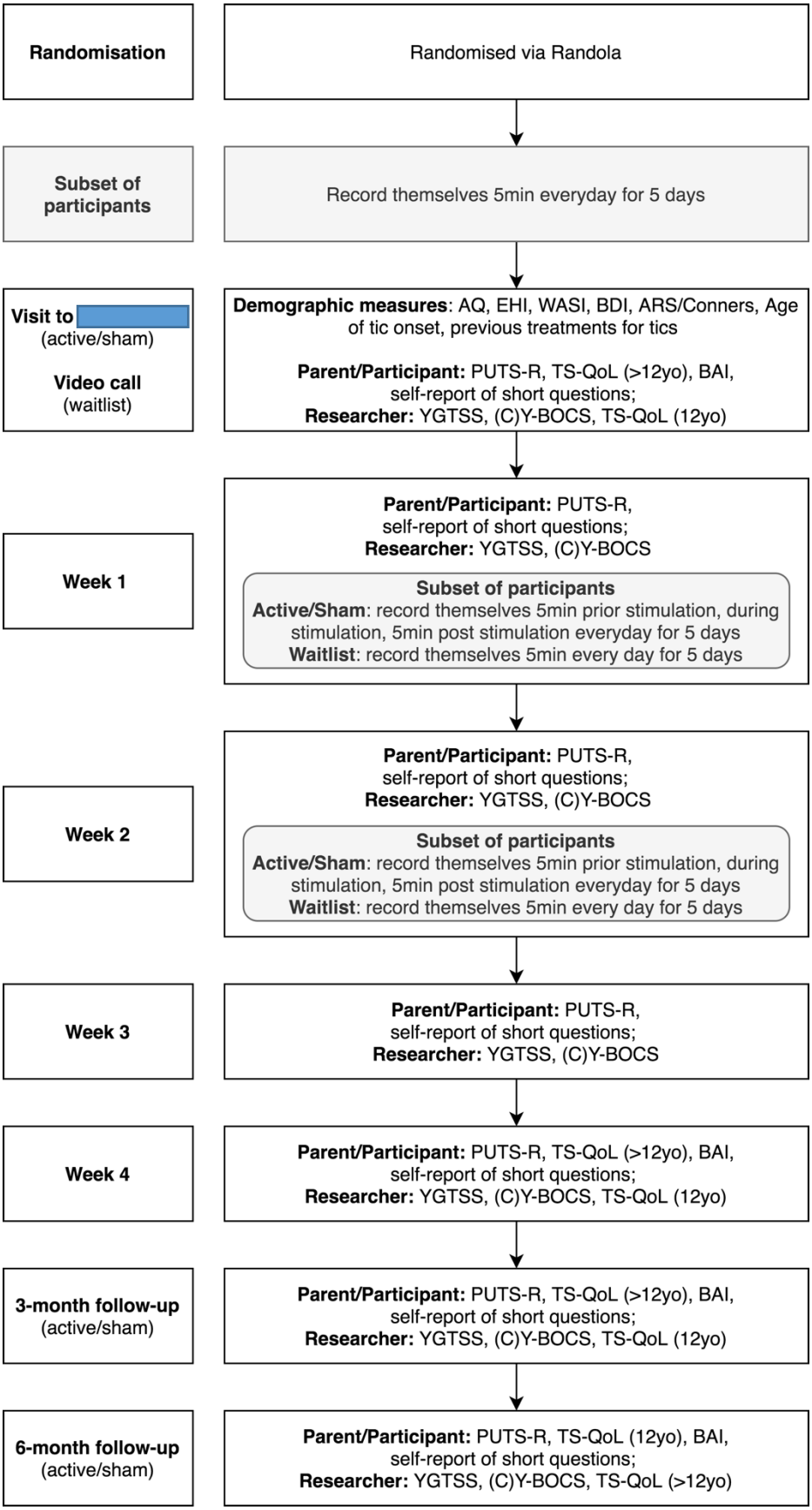

Figure 2. Schematic flow diagram of the trial measures

Statistical analyses and data processing

In this section we outline the main statistical analysis and data processing approaches that we propose to run for this trial. Our preference is to use parametric statistics and Bayesian hypothesis testing and report effect sizes when appropriate. However, if the data violate the required assumptions, suitable non-parametric equivalent approaches such as Mann-Whitney U-tests, Kruskal-Wallis tests, or permutation testing will be utilised.

Demographic information:

Demographic data will be summarised by group. Continuous data within groups will be reported as mean (SD) or median, when skewed. Categorical data within groups will be reported as a percentage. Statistical analyses will be performed on these data to identify any demographic differences between groups.

Primary outcome analyses: Change in tics indicated by YGTSS-TTS score

Change in total tic severity score from the YGTSS scores over time (baseline, weeks 1, 2, 3 and 4) will be analysed using multivariate linear regression techniques to determine the extent that changes over time in tic severity can be predicted by demographic and clinical measures.

Differences in scores between *timepoints* and between *groups* will be analysed with an ANOVA or if required, a non-parametric equivalent. Significant interactions will be followed-up using a t-test. Differences between scores in the 3-month and 6-month follow-up periods between the active and the sham groups will be analysed using a t-test or non-parametric equivalent test as appropriate.

Secondary outcome analyses: Change in impairment, quality of life, premonitory urges, OCD symptoms and anxiety

Overall impairment rating on the YGTSS, premonitory urges using the PUTS, OCD symptoms using (C)Y-BOCS, anxiety using BAS and well-being using QoL-TS will be assessed as follows. Similar to the primary outcome, change in scores over time (baseline, weeks 1, 2, 3, and 4) will be analysed using linear regression or suitable alternative, if relevant assumptions are not met. Difference in scores between timepoints and groups will be analysed using ANOVA. Significant effects will be followed up using t-tests corrected for multiple comparisons when necessary. Difference in scores in the 3-month and 6-month follow-up periods between the active and the sham groups will be analysed using a t-test or non-parametric equivalent.

Exploratory analyses:

Regression analyses will be used to explore potential relationships between scores from questionnaire measures (including sub scores on YGTSS) and changes in tics. This will allow us to explore how factors such as medication and comorbidity interact with tic change across the different groups. A subgroup analysis including children and adolescents will be performed as tics in this group can fluctuate.

Video data analyses:

As analysis of video data is extremely time consuming, we will reduce the data prior to statistical analysis as follows. For each week, 3 of the possible 5 recordings will be selected at random for further analysis. A start time will be randomly generated, and a 2-minute segment from this time point onward will be assessed. The same time points will be assessed for each of the videos selected for that week. Videos collected during the 5 day baseline and all videos from the waitlist group will be 5 minutes long and will be processed as above. Videos collected during the active and sham stimulation phase will be consist of 5 minutes before stimulation, 14 minutes during which stimulation is delivered, and 5 minutes after stimulation has ceased. For these videos, 2 minutes segments from each of these three time periods will be randomly selected for assessment. The selected 2 minutes segments from the 14 minutes during which stimulation is delivered will belong to a 2 minute period when the stimulation was on.

This approach to data reduction will generate a total of 6 minutes of baseline video for each participant regardless of groups. From the subsequent two-week period of recording, data reduction will result in 12 minutes of video for each participant in the waitlist group and 36 minutes for each participant in the sham and active groups. For each participant in the active and sham stimulation groups, the 36 minutes of video data will consist of 12 minutes prior to, 12 minutes during and 12 minutes after stimulation. The number of tics will be averaged between the videos taken on the same week and within the same period of stimulation session (i.e. prior, during or after stimulation). Tic count training will be conducted by a highly experienced researcher and those individuals coding video will count 1.5 times the total of the videos to create overlap between codes and permit assessment of coder reliability.

In order to assess online effects of the stimulation, data will first be averaged across video segments resulting in a single value for each participant for before, during and after stimulation. Data will be analysed using a mixed models ANOVA with group (sham/ active) and time of measure (before/ during) entered as between and within subjects' factors respectively. Any significant effects will be followed up using t-tests (with necessary adjustments if needed). A second ANOVA and relevant follow up statistics will be used to assess changes between tics counted during and following stimulation.

In order to measure the treatment effects of the stimulation, we will examine the difference in the average number of tics between baseline and pre-stimulation period (or no stimulation in the waitlist group) of the first week and baseline and pre-stimulation period (or no stimulation in the waitlist group) of the second week using an ANOVA. Any significant effects will be followed-up using t-tests (adjusted for multiple comparisons). Change in scores over time (baseline, pre-stimulation/no stimulation week 1, pre-stimulation/no stimulation week 2) will be analysed using a linear regression.

In addition to this, we intend to conduct additional exploratory analyses. Specifically, scores following active stimulation in the waitlist group will be compared to the active group to examine any open-label effects. If there are no statistically significant differences between these two groups, the data will be combined for further within-subjects analysis.

Safety/ adverse events

There are no adverse events or side-effects expected. Any reported adverse events will be recorded and monitored.

Ethics

This study was approved by the appropriate Ethics Committee at the University of Nottingham on 15/12/2020 (REF: F1273).

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