

Study Title: Investigating Non-invasive brain Stimulation To Enhance fluency in People who stutter

Short title: INSTEP Trial

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All the investigators declare that there are no conflicts of interest associated with the proposed study.

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1. SYNOPSIS

Study Title	Investigating non-invasive brain stimulation to enhance fluency in people who stutter
Internal ref. no. / short title	INSTEP Trial
Study Design	Double-blind randomised controlled trial. Active treatment: bi-hemispheric tDCS, Control: Sham tDCS. Minimisation randomisation.
Study Participants	Healthy adult males with developmental stuttering and healthy male controls with no speech disorders
Planned Sample Size	70 (40 participants with developmental stuttering, 30 control participants)
Planned Study Period	1 st November 2017 – 30th April 2020
	Outcome Measures
Primary	Change from baseline (i.e. baseline subtracted) in a clinical measure of stuttering severity (SSI-4), post training (1 week, 6 weeks, and 3 months after training).
Secondary	Change from baseline (i.e. baseline subtracted) in: (i) % disfluent syllables produced during conversation; (ii) % disfluent syllables produced during reading post training (1 week, 6 weeks, and 3 months after training). (iii) total score on an attitudinal measure (OASES), post training (6 weeks, and 3 months after training).
Other Pre-specified	Change from baseline (i.e. baseline subtracted) in: (i) total score on the Premonitory Awareness in Stuttering Scale; (ii) total score on the Beck Anxiety Inventory; (iii) subjective and objective ratings of stuttering severity and naturalness, post training (1 week, 6 weeks, and 3 months after training). Changes from baseline (i.e. baseline subtracted) % disfluent syllables produced during (i) conversation and (ii) reading, during the 5-day training (immediately post intervention days 1 to 5; immediately pre-intervention days 2 to 5).
	Exploratory (non-behavioural) measures
Other	We will use MRI and TMS, to evaluate neural structure, function, and excitability in people who stutter and in healthy controls. Using MRI, we will also obtain images of the vocal tract during speech. These measurements will be obtained just before training begins and 1 week after the end of the training in people who stutter and once only in healthy controls.

2. ABBREVIATIONS

BAI	Beck Anxiety Inventory
CI	Chief Investigator

DS	Developmental Stuttering
fMRI	Functional magnetic resonance imaging
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDREC	Interdisciplinary Research Ethics Committee
MRI	Magnetic Resonance Imaging
OASES	Overall Assessment of Speaker's Experience of Stuttering
OHBA	Oxford Centre for Human Brain Activity
PAiS	Premonitory Awareness in Stuttering Scale
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PWS	People who Stutter
REC	Research Ethics Committee
rsfMRI	Resting state functional magnetic resonance imaging
SOP	Standard Operating Procedure
SSI-4	Stuttering Severity Instrument, 4 th Edition
TCS	Transcranial Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation

3. BACKGROUND AND RATIONALE

Developmental stuttering is a disorder affecting the fluency of speech, characterized by repetitions or prolongations of sounds and frequent hesitations or pauses. It affects 5% of children and persists to adulthood in about 1%. Changing the way speech is produced in adults who stutter is a particular challenge for speech and language therapy and there is a need for novel interventions, therefore. One such intervention involves the application of transcranial direct current stimulation (tDCS) alongside speech therapy. tDCS influences brain activity by modulating neuronal plasticity through the application of weak electrical currents across the brain. Pairing tDCS with speech therapy has potential for producing larger or longer lasting effects and reducing time spent in therapy. In a previous study, we showed that a five-day training regime of anodal tDCS combined with temporary fluency enhancers led to improvements in speech fluency in PWS that were sustained for five weeks post intervention.

The first aim of our study is to replicate our previous finding using a slightly different form of tDCS combined with speech fluency training to improve outcomes in people who stutter (PWS). We will use metronome-timed speech to temporarily induce fluency during the training. PWS will have this training for 40 minutes a day while receiving anodal tDCS over the left frontal cortex and cathodal tDCS over the right frontal cortex for five consecutive days (1mA for 20 mins at the start of the intervention on each day) in a double-blind randomized controlled trial. Outcomes

will be measured in terms of changes to stuttering severity, dysfluency rates for reading and conversation, naturalness ratings, and attitudes to stuttering.

The second aim of our study is to understand how changes in the interactions between sensory and motor regions of the brain relate to changes in speech fluency in PWS. We will use MRI to measure brain structure and function. We will also image the vocal tract during speech production. Transcranial magnetic stimulation (TMS) will evaluate changes in excitability of the motor system underlying speech production. These studies are exploratory measures of the intervention in PWS.

4. STUDY DESIGN

This is a double-blind, placebo-controlled (sham tDCS), randomised trial, with 20 participants with developmental stuttering recruited for each arm of the trial. The participants will be expected to complete at least two visits to the OHBA imaging centre in Oxford (at baseline and at the +1 week follow up) for the assessments of neural structure, function, and to assess movements of the vocal tract (MRI, TMS, & vocal tract imaging). In addition, participants will complete one live interaction and one videoconference at baseline and at +1 week follow up, complete training for 5 days, and engage in two more videoconference interactions for follow-ups (6 weeks and 3 months after the end of training), which will involve doing reading and conversation tasks so speech fluency can be assessed. The researchers can travel to the participant's home or office for the live components of these visits as well as the tDCS + speech fluency training. In total, participants will have 9 visits over a 5-month period. A flowchart illustrating the study design is included in Appendix A.

5. PARTICIPANT IDENTIFICATION

5.1. Study Participants

Adult male participants with developmental stuttering of mild-moderate severity (as ascertained by a total score of greater than 20 on the stuttering severity instrument – version 4 [SSI-4]) and healthy male volunteers aged 18-45 years.

5.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male, aged 18 years or above.
- Diagnosed with developmental stuttering of mild-moderate or greater severity
- Native speaker of English
- Normal or corrected-to-normal vision
- Normal hearing

5.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Speech, language or communication disorder other than developmental stuttering.

- Contraindication to brain stimulation (tDCS or TMS)
- Contraindication to MRI
- History of drug abuse
- History of a neurological or psychiatric illness
- Any previous neurosurgical procedures
- Taking prescription or over-the-counter medication that may affect brain function (for example, anti-depressants)
- Family history of epilepsy (first degree relative)
- Severe claustrophobia (as they may be unable to tolerate scanner)

The inclusion and exclusion criteria for **the control group** of participants are as above, with the exception that developmental stuttering will be an exclusion criterion.

6. STUDY PROCEDURES

6.1. Recruitment

Volunteers who self-report stammering/ stuttering will be recruited for the study, in addition to an age- and gender-matched control sample.

We will advertise the study within the university through traditional channels, for instance, on departmental mailing lists and posters located in University Departments (including at Oxford Brookes), social media channels, to the departmental participant pool, as well as on noticeboards in colleges affiliated with the University. We will also place advertisements in the local community (e.g. in community centres, sports centres etc.). In addition, we will recruit through self-help and advocacy groups for people with stammering, such as the British Stammering Association. With their permission, we will post advertisements in their newsletters/ magazines, advertise our study via their social media channels (such as Twitter or Facebook), and also place our advertisement on noticeboards within physical spaces they use.

Some participants may be recruited by 'word of mouth', by which we mean they may contact us having heard about our research in conversation with a previous participant or other person, or following a conversation with a member of our research team, or through media coverage.

We will provide study information to anyone expressing an interest in participating. Further information about the study will also be available on our website. We will only be able to enrol participants who are eligible for the study. Should volunteers express a desire to participate, they will undergo the screening and eligibility assessment outlined below.

6.1. Screening and Eligibility Assessment

When a person who stutters contacts the research team and expresses a desire to participate, they will be sent the PIS outlining the procedures and risks involved in taking part. Screening will take place before volunteers have consented to take part in the study. The screening procedure involves obtaining information in line with tDCS, TMS, and MRI safety guidelines (outlined in the standard operating procedure documents developed within the Medical Sciences Division). Also see exclusion criteria in section 6.3 of this protocol. Screening criteria will be assessed by self-report.

Volunteers will also complete a screening assessment of stuttering severity to ascertain eligibility. In the first instance, one of the named investigators will conduct a screening by videoconference (Skype) to determine severity. Stuttering symptoms are typically increased on the first meeting (when participants are unfamiliar with their conversation partner) and over the telephone/ during videoconferencing. Consequently, if stuttering is determined to be of mild severity at this stage, the volunteer will be informed that they do not meet the inclusionary criteria for the study. If stuttering is of mild-moderate or greater severity, a face-to-face appointment will be scheduled, which will take place on University premises, or at the participant's home or office. The severity of stammering as ascertained on this visit will be used to determine whether participants should be enrolled into the study. If stuttering is of mild-moderate or greater severity, then they will be invited to participate.

Once we have determined eligibility, informed consent will be obtained and a suitable appointment will be scheduled, within three months of the screening. If the participant is deemed ineligible, we will first enquire if they wish to participate in other studies within the lab for which they might be eligible. If they do not, all screening data will be deleted (within a month of notification of ineligibility).

6.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been delegated responsibility by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

6.3. Randomisation, blinding and code-breaking

A 'minimisation' sampling procedure will be used, whereby participants' stuttering severity as measured during screening with the SSI-4 will be used to assign successive participants to true stimulation or sham stimulation, minimising group differences in severity. A member of the Departmental of Experimental Psychology who is not involved with the study will be in charge of communicating to the project team what code they should use.

On the basis of this randomisation, half the participants will receive true tDCS stimulation and the other half will be in a control group that will not receive stimulation (sham tDCS). In sham tDCS the current is applied for a sufficiently brief duration to avoid any change in cortical

excitability (up to 30 seconds) but long enough to produce the transitory sensation on the skin associated with real tDCS. Although the stimulation is different, each participant will receive exactly the same speech training throughout the study.

The study will also be double-blinded, meaning that the researchers, study staff, and participants will not know whether the condition involves real or sham tDCS. The stimulator used in the study has a 'study' mode to allow the operator to be blind to the stimulation condition.

The person in charge of the randomisation procedure will have the capacity to unblind the data for analysis once data collection is complete. Data may be unblinded during the data collection only in the context of a serious adverse event potentially related to the type of stimulation or if a patient withdraws from the study and needs to be replaced.

6.4. Baseline Assessments

Following the screening to determine eligibility, participants will complete the baseline assessments (Visit 1, Days 1-2). This visit will take place at OHBA.

During this visit, we will obtain informed consent. We will obtain behavioural measures of speech fluency, as well as complete clinical assessments (SSI-4, OASES). Following this, participants will complete the brain and vocal tract imaging assessments (MRI and TMS) as described below.

6.5. Subsequent Visits

Visits 2-6 [Days 3-7]

These visits may take place at University testing facilities, or at the participant's home or office and will take place at the same time on each day. Participants will complete a short speech fluency assessment during reading and conversation at the start and end of the session; this assessment will be video recorded. A safety screening for tDCS will be conducted to ensure that the participant is not experiencing any discomfort/ risk, and to check that eligibility has not been compromised (for example, by use of medication). The intervention will then be delivered (sham vs. true tDCS + speech fluency training). The speech fluency training lasts approximately 40 minutes and stimulation is delivered for 20 minutes at the start of the training. Each session should last no more than one hour on each of the five days of intervention.

Visit 7 [Days 14-15]:

This visit will take place at OHBA. We will obtain behavioural measures of speech fluency, as well as complete clinical assessments (SSI-4). Following this, participants will repeat the brain and vocal tract imaging assessments (MRI and TMS) described. Standard operating procedures and safety guidelines for each of these procedures will be followed.

Visit 8 [+6 weeks following Visit 6]

This visit will be conducted via videoconference. We will obtain behavioural measures of speech fluency, as well as complete clinical assessments (SSI-4, OASES).

Visit 9 [+3 months following Visit 6]

This visit will be conducted via videoconference. We will obtain behavioural measures of speech fluency, as well as complete clinical assessments (SSI-4, OASES).

6.6. Description of procedures

Brain stimulation intervention [over 5 days]

tDCS

Once contraindications to transcranial direct current stimulation (tDCS) are excluded, the risks of taking part in a tDCS study are minimal. An experienced researcher will go through a list of possible risks with the participant before the study and answer any questions. TDCS directly and non-invasively stimulates the brain through the application of electrical currents to a small region of the scalp. The current is generated by a battery-powered stimulator and passed through rubber electrodes and conductive material (gel or saline-soaked sponges). At least one electrode is attached to the scalp with a band. The other electrode may be positioned on the scalp also or on the body (e.g. shoulder). The electrode size of the stimulators in use by research groups at present is large (~25-35 cm²) and the current strengths used are low (~1-3 mA) resulting in very low current densities (0.029 - 0.12 mA/cm²). The possible minor side-effects of tingling, itching or a mild burning sensation under the electrode are more likely with the higher current densities so are less desirable. Typical protocols apply no more than 20 minutes of stimulation in a single session. During the whole duration of the experiment, the participant is able to talk with the researchers and indicate any discomfort. The participant will be assured that they can withdraw from the study for any reason without penalty. In this study, we will use tDCS with 35 cm² electrodes placed over the frontal cortex bilaterally (channels FC5 and 6 electroencephalography). A 1-mA current will be used, ramped up over 30 seconds and applied for 20 minutes at the start of the speech fluency training. For the sham stimulation, the stimulator will ramp up the current to 1 mA over 30 seconds and then turned off. In study mode, the stimulator continues to test the impedance of the electrodes. This ensures that the researcher and the participant remain blind to stimulation condition.

Speech fluency assessments [All visits]

Participants will complete a reading and conversation task on each of the visits. These will be video- and audio-recorded, and scored offline by members of the investigation team for instances of dysfluency.

Brain and vocal tract assessments [at baseline and at follow up one week after training]

Brain stimulation techniques

TMS

TMS is a technique that allows us to stimulate the brain by rapid switching of a magnetic field in a coil placed over the head. Once contraindications to TMS are excluded, the risks of taking part in a TMS study are minimal. An experienced researcher will go through a list of possible risks with the participant before the study and answer any questions. The effects of TMS can be assessed by recording the activity of muscles (electromyography; EMG). EMG activity of the

muscle is measured at the surface of the skin by attaching an electrode (small silver disc). In order to record this activity, several electrodes will be taped on the skin over muscles of a participants' hands and lips. During TMS, a coil is positioned over the scalp and single pulses are used to stimulate the brain. The intensity of stimulation is varied until the EMG recording consistently shows activity in the muscle in response to the stimulation. Once the minimum intensity at which this activity is observed is determined, the experiment begins. We will use single pulses (suprathreshold) of TMS to measure the excitability of the motor cortex during speech perception and to assess interhemispheric connectivity. During the experiment, which would last no more than one hour, the participant is able to talk with the researchers and indicate any discomfort. The participant will be assured that they can withdraw from the study for any reason without penalty.

Imaging techniques

MRI

Imaging interventions: Once contraindications to magnetic resonance imaging are excluded by use of the facility's screening forms, the risks of undergoing a scan are minimal. A trained scanner operator or radiographer will go through a list of possible risks with the participant before scanning. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionising radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants' clothing, jewellery (such as body piercings), or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners. During the actual scanning procedure, the scanner produces loud banging noises and the participant will be given suitable hearing protection (earplugs). There is a small mirror that will allow them to see out of the scanner. During the experiment, the participant will be able to communicate with the operator in the control room. In addition, they will be given a call button, which allows them to alert the operator at any time. People with a history of claustrophobia may be excluded from participation in the study. All participants will still be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants will be able to indicate immediately if they wish the scanning to cease by pressing a call button in their hands.

The MRI session will last 90 minutes and participants will be allowed to come out of the scanner for a break if needed. Participants will be asked to lie still but remain awake during resting state scans. During structural image acquisition, they may watch a video of their choice or listen to music or radio. For the functional tasks, they will be given instructions and have the opportunity to practise the tasks outside the scanner to be sure that they understand what is required. Tasks will be simple and involve making button presses or speech responses to stimuli and listening to sounds. During the vocal tract imaging, participants will be asked to repeat words, non-words, and sentences. They will hear themselves speaking via headphones and sometimes this feedback will be altered.

Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

The reason for withdrawal will be recorded in the Case Report Form. We will replace participants who withdraw from the study, if we are able to do so. With permission, we will use the data of subjects who have withdrawn from the study, if it is usable (e.g. we may use behavioural, neural, or vocal data data that was collected until participant withdrew to evaluate our tertiary objectives). If we do not have the participants' permission to use the data, we will exclude it from our analyses, and all data and information collected from those participants will be securely destroyed.

6.7. Definition of End of Study

The end of study is the date of the last follow up (videoconference) of the last participant.

7. INTERVENTIONS

A five-day intervention with tDCS (bi-hemispheric vs. sham) combined with speech fluency training will be carried out.

tDCS: Participants will receive five daily sessions of real tDCS combined with speech training, or sham stimulation combined with speech training, according to which arm of the trial they are randomly assigned. Stimulation will be applied for no more than 20 minutes per session. Stimulation will be carried out in accordance with the protocol for the Central University Research Ethics Committee for use in healthy volunteers. Our study will be carried out in accordance with procedures outlined in the SOP and will not exceed the recommendations of the approved protocol. Please see section 7.6 for addition information regarding tDCS procedure.

Speech fluency training: Participants will complete speech tasks whilst speaking to an external beat (metronome-timed speech). Different tasks will be used during the 20 minutes of stimulation and repeated for a further 20 minutes once the stimulation has ended. The order of tasks will be randomised across the five days of speech training. The duration of each training session will be one hour, and participants will receive concurrent tDCS for 20 minutes at the start of the fluency training. Participants will also complete brief speech tasks before and after the training.

8. SAFETY REPORTING

8.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the Medical Sciences IDREC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. In addition, these events will be reported to the relevant safety officers at OHBA and the Department of Experimental Psychology. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

9. STATISTICS AND ANALYSIS

9.1. Description of Statistical Methods

Behavioural data measuring the primary outcome (speech function) will be acquired before, during and after brain stimulation using audio and video recordings. Measures of speech fluency (e.g. Stuttering Severity Instrument score, % disfluency) will be taken from these recordings and will be subjected to standard statistical analyses using software such as SPSS. Mixed between- and within-subject designs will be used to compare changes in performance (baseline subtracted) on speech measures between the two groups of participants (tDCS vs. sham). The investigator team have prior experience in statistical analysis of similar behavioural data.

Brain imaging data (MRI) will be analysed using the FMRIB Software Library (FSL) which involve standard approaches for the analysis of functional imaging data. We will also be using novel approaches that allow us to explore functional connectivity, such as probabilistic Independent Component Analysis. The investigator team has substantial with MRI analysis using FSL and SPM.

Vocal Tract Images will be analysed using custom tools implemented in MATLAB.

TMS data will be analysed using custom tools and software to compare measures of cortical excitability within participants between hemispheres, and across time points, and between groups at the baseline timepoint.

While the study is ongoing, we will be able to compare brain and vocal tract imaging, and TMS data in PWS vs controls once we have data from the baseline timepoint. Unblinding is not required for these baseline analyses.

9.2. The Number of Participants

We plan to recruit 40 PWS and up to 30 controls. The sample size was determined based on previous cross-sectional studies in stuttering, including our own. A sample size of 20 participants in each group is higher than most previous behavioural and functional imaging studies in PWS. This should ensure sufficient sensitivity to detect differences in behaviour, brain structure and function. It should also allow us to determine the relationship between the experimental variables and other measures such as stuttering severity and duration of stuttering. A sample size of 20 for each group should detect a group difference with an effect size of 0.9 at 80% power and 5% false positive rate. For the tDCS study across 5 days, we will compare two groups of 20 PWS. In our previous study, with sample sizes of 15 in each group, effect sizes of 0.93 and 0.50 were obtained for the reduction in the SSI at 1 week and 6 weeks post intervention.

9.3. Analysis of Outcome Measures

Only data from participants who have not withdrawn consent will be included in final analyses. If participants drop out, we will attempt to replace their participation.

We will compare measures of speech function based on standardized tests and measures of speech fluency from speech samples. The primary outcome is defined as change in SSI-4 score (baseline subtracted), and the secondary outcomes are change in % disfluency and OASES score.

Differences between sham and tDCS intervention in brain imaging measurements will be evaluated using standardized analysis tools in the FMRIB Software Library. In functional MRI our outcome measures are the intensity and size of activation clusters based on the recorded blood-oxygenation-level-dependent signal (BOLD) that are involved in the tasks we ask participants to complete. Structural image analysis will be employed to measure white matter diffusion and grey matter morphometric differences in areas identified as abnormal in previous studies of stuttering.

Vocal tract imaging data will be analysed using custom tools to calculate the range of positions in tongue blade movement, lip protrusion, and laryngeal lowering during speech production. We predict that spatiotemporal variability in these movements will be greater in PWS compared with controls and reduce in those with measureable improvements in fluency following speech training.

The motor excitability and measures of cortical connectivity obtained using TMS and MEPs will be compared in PWS and Controls and at baseline relative to week 1 to examine for correlates of improved speech fluency in PWS.

We will compare differences in brain and vocal tract imaging data in PWS and controls. Only data from the baseline time point will be used.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and any host institution for monitoring and/or audit of the study to ensure compliance with regulations. We also expect our results will be published in a scientific journal and that anonymised data will be uploaded to recognised open data repositories at the end of the study (such as openfMRI) at

the end of the study. Video recordings will be made of participants speaking and this is the basis of our primary outcome measure. The video/audio data collected in this study will not be shared on data repositories, as it cannot be sufficiently anonymised. We would not normally give feedback about results to individual participants.

10.2. Data Recording and Record Keeping

All study data will be kept strictly confidential. A unique study specific number i.e. a code will identify the participants in databases created for the study, and identifying information associated with this code will be stored in a locked filing cabinet in the Department of Experimental Psychology. Names and any other identifying detail will NOT be included in any study data electronic file.

Brain imaging and stimulation data will also be anonymised using the study specific code and will be stored on password-protected computers in the Department of Experimental Psychology or OHBA respectively and backed up on hard disks. Video/audio recordings of the participant will also be associated with this code and backed up on Departmental servers. Data will be stored for 5 years following the final publication related to the study.

Students and collaborators may be given access to fully anonymised data and the video recordings under the supervision of the named investigators and with approval of the Chief Investigator. Some peer-reviewed journals require submission of anonymised data and anonymised data may also be uploaded to other data sharing initiatives. Access may be given to responsible members of the University of Oxford for the purposes of monitoring or audit.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The PI and named investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The PI and named investigators will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Medical Sciences IDREC and host institution for written approval.

The PI and named investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

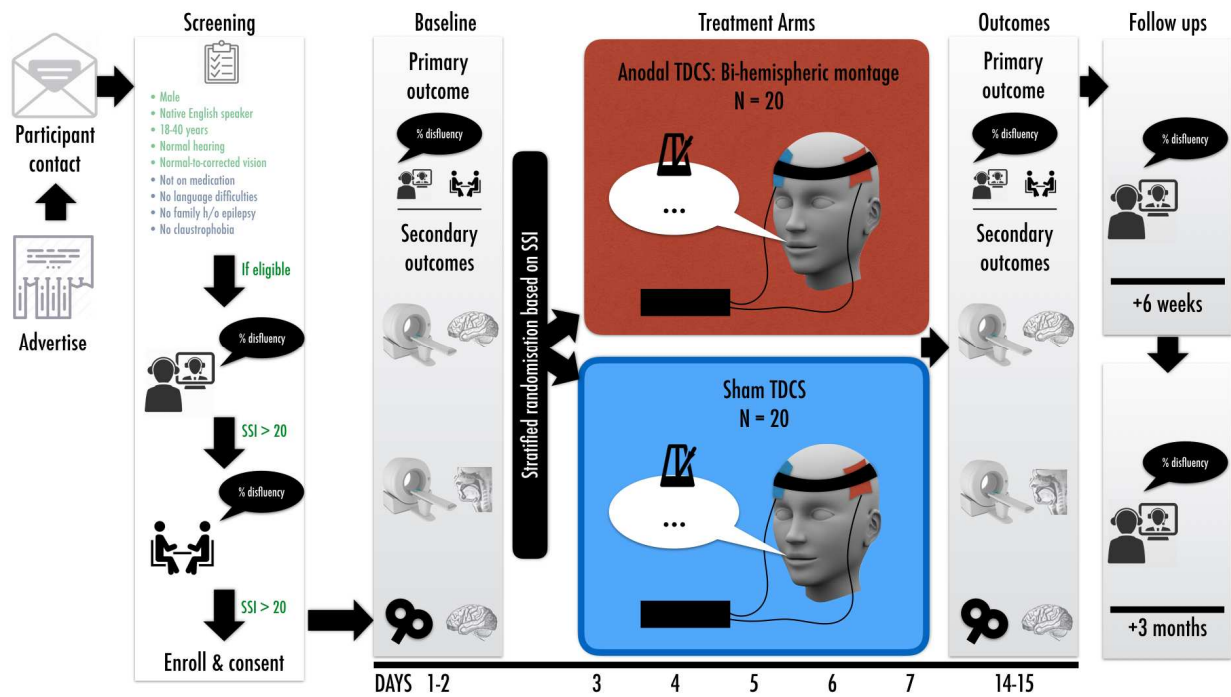
Personal data may be retained after the end of the study where the participant agrees to be contacted for future studies. This information will be unlinked to the study data. For volunteers who do not wish to be contacted in the future, personally identifiable data will be shredded as soon as possible after completion of the study and within one year of completing study analyses.

12.5. Expenses and Benefits

The study investigates the potential for a therapeutic benefit of tDCS in stuttering, so participants in the study may expect an immediate direct benefit. We will explain in writing in PIS that no direct benefit can be guaranteed, and also re-iterate this verbally during the study screening process.

Participant will be reimbursed for their time and effort: PWS will get £180 for completing the study (2 x MRI, 2 x TMS; 5 x TDCS) and a control would get £40 (1xMRI + TMS). Should any participant withdraw from the study for any reason, they will be paid for their time up to that point at the rate of £10/ hour. In addition, participants who complete any screening visits but are not deemed eligible for the study will be paid £10/hour for their time and effort. Reasonable travel expenses for any visits will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

APPENDIX A: STUDY FLOW CHART



APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Visits									
	Visit 0 Day 0	Visit 1 1-2	V2 3	V3 4	V4 5	V5 6	V6 7	Visit 7 14- 15	Visit 8 +6 weeks	Visit 9 +3 months
	Screening	Baseline	Training					Follow up		
Informed consent		X								
Demographics	X	X								
Eligibility assessment	X	X								
Randomisation		X								
tDCS			X	X	X	X	X			
Speech (videoconference)	X	X						X	X	X
Speech (Live)		X	X	X	X	X	X	X		
SSI-4	X	X						X	X	X
OASES		X							X	X
MRI brain		X						X		
TMS brain		X						X		
MRI vocal tract		X						X		
Adverse event assessments		X	X	X	X	X	X	X		
BAI		X						X	X	X
PAIS		X						X	X	X
Subjective speech ratings (severity & naturalness)		X						X	X	X
Objective rating of naturalness		X	X	X	X	X	X	X	X	X