Noninvasive brain stimulation in adults who stutter

NCT03437512

2-25-2021

Non-invasive brain stimulation in adults who stutter

Principal investigator: Emily O. Garnett, PhD., Department of Psychiatry, University of Michigan

Co-Investigator: Soo-Eun Chang, PhD., Department of Psychiatry, University of Michigan; Ho Ming Chow, PhD., Department of Psychiatry, University of Michigan; Benjamin Hampstead, PhD., Department of Psychiatry, University of Michigan.

Objective

Research studies in stuttering have shown that activity patterns in certain brain areas differ in people who stutter compared to people who do not stutter when speaking. The purpose of our study is to investigate how mild, non-invasive brain stimulation applied consecutively for five days affects speech relevant brain areas, which may in turn affect speech fluency and speaking-related brain activity in people who stutter. The long-term goal of this study is to test the therapeutic potential of transcranial direct current stimulation (tDCS) for the treatment of stuttering.

Contents

1. Specific Aims

1.1. Specific Aim #1: Determine effects of anodal HD-tDCS targeting left pSTG on speech fluency in adults who stutter. Pre-training measures of stuttering severity (e.g., percent stuttering-like disfluencies, OASES scores) will be compared with those same measures immediately following training, as well as 4 weeks post-training. We hypothesize that when paired with a fluency-inducing speech condition, active stimulation targeting left pSTG will lead to a greater increase in speech fluency compared to behavioral training alone (sham stimulation).

1.2. Specific Aim #2: Determine effects of anodal HD-tDCS targeting left pSTG on performance on rhythm judgement tasks. Pre-training measures of performance (reaction time and accuracy) on finger-tapping tasks and rhythm judgment tasks will be compared with those same measures immediately following training, as well as 4 weeks post-training. We hypothesize that when paired with a fluency-inducing speech condition, active stimulation targeting left pSTG will lead to a greater increase in performance on these tasks compared to behavioral training alone (sham stimulation).

1.3. Specific Aim #3: Determine effects of anodal HD-tDCS targeting left pSTG on functional connectivity within BGTC regions during speech production. Pre-training measures of functional connectivity within BGTC regions will be compared before and immediately following training, as well as 4 weeks post-training. We hypothesize that when paired with intensive training under fluency inducing conditions, active stimulation targeting left pSTG will lead to increased functional connectivity within the BGTC network compared to behavioral training alone (sham stimulation).

2. Significance & Background

Developmental stuttering is a disorder of speech fluency affecting approximately 5% of preschool-age children. Up to 20% of these children continue to stutter well into adulthood (Yairi & Ambrose, 2013). Conventional treatments aim to improve fluency through behavioral strategies such as slow rate, prolonged speech, and easy onsets (Bloodstein & Ratner, 2008). A considerable amount of time and effort (> 100 hours) is needed to significantly improve fluency

(Andrews, et al., 1980), and over 70% of those treated experience relapse, particularly adults (Craig & Hancock, 1995; Craig, et al., 1996; Hancock et al., 1998). Success with delayed feedback is variable and short-lived (Foundas et al., 2013), and pharmacological treatments are largely ineffective and associated with side effects (Bothe et al., 2006; Maguire et al., 2010). Given that AWS often experience emotional, social, and vocational difficulties throughout their lives, there is a critical need for developing therapeutic interventions that result in long-term enhancement of speech fluency in people who stutter. There is accumulating evidence of subtle neural differences in people who stutter, and that the use of non-invasive brain stimulation improves motor and language performance. We propose to test if pairing stimulation with training will lead to effective, longer lasting increases in speech fluency and brain connectivity within related neural networks in AWS, beyond that of speech training alone (i.e., sham stimulation).

2.1. <u>Applying an established theoretical framework and empirical data from neuroimaging to guide novel intervention research in stuttering.</u> Motivated by a neurobiologically plausible model of speech production (Gradient Order Directions into Velocities of Articulators [GODIVA]; Bohland et al., 2010) research suggest that stuttering may stem from disruption in the basal ganglia thalamocortical (BGTC) network, specifically in the connections among the basal ganglia (BG), supplementary motor area ([SMA]) and ventral premotor cortex ([vPMC]; Civier et al., 2013; Fig 1.). The disruption in the BGTC network affects coordination of precisely-timed movement initiation (subserved by SMA), activation of speech sounds (subserved by vPMC), and sequencing of sounds (subserved by BG), considered required to produce fluent speech. The SMA is considered critical in planning over-learned, complex movement routines, including speech production, that are *internally timed and initiated*, rather than in response to external cues (Cunnington et al., 1996; Packman et al., 2007). One interpretation is that SMA assists with coordinating the timing of speech movements through connections with the motor system (Bohland & Guenther, 2006). GODIVA hypothesizes that stuttering is a result of delayed activation of the upcoming syllable's motor plan. Indeed, people who stutter demonstrate difficulty in preparing and controlling precisely-timed complex movements, including initiation of propositional speech (Packman & Onslow, 2002). Further, both AWS and CWS demonstrate poor performance on non-speech tasks that involve timing and rhythm (Wieland et al. 2015a, 2015b, 2016; Chang et al. 2016) and attenuated functional connectivity among BGTC network regions (Chang & Zhu, 2013, Lu et al., 2009; 2010).

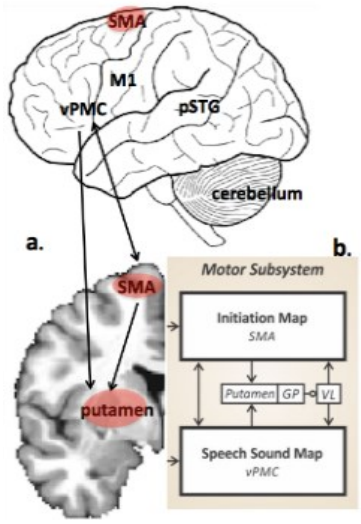


Figure 1. a Basal ganglia thalamocortical network (BGTC) structures in red). b. Motor subsystem in GODIVA model releases planned speech movements (both cortical and subcortical areas). Speech sound map in ventral premotor cortex (vPMC) provides input regarding sensorimotor programs to putamen, involved in sequencing motor movements. The initiation map in SMA aids in initiation of movement for speech production, and is structurally connected with putamen.

2.2. <u>Effects of fluency-inducing conditions on behavioral and brain measures.</u> If the overt disfluencies in stuttering are reflective of disrupted connectivity within BGTC network regions, there is at least some evidence that the application of *external* timing cues can significantly decrease stuttering (i.e., increase fluency) by acting on this 'timing network'. Most speakers who stutter exhibit temporarily increased fluency during conditions that include an *external* pacing element, such as choral speech or with a metronome (Park & Logan, 2015). Such techniques are also associated with more 'normalized' brain activation patterns (i.e., similar to activation patterns found in nonstuttering speakers), such as increased left frontotemporal activation, and reduced motor activation, including right frontal opercular areas, as well as increased pSTG (De Nil et al., 2003; Giraud et al., 2008; Kell et al., 2009; Neumann et al., 2005; Toyomura et al., 2011; 2015). Giraud et al. (2008) found that activity in the basal ganglia was correlated with stuttering severity before, but not after, 3 weeks of speech fluency training. This suggests that therapy can modulate brain activity in regions within the proposed 'timing network' focused on in this proposal. If, at its core, stuttering reflects an internal timing deficit that impacts the precise initiation of speech movements leading to overt disfluencies, this would suggest that the BGTC circuits, including SMA-putamen and pSTG, are functionally

aberrant in stuttering. Therefore, we aim to augment improvements in fluency through the modulation of functional connectivity within BGTC by pairing noninvasive brain stimulation to pSTG with an induced fluency condition, as increases in activation in pSTG have been shown to support improved speech fluency.

2.3. Potential impact of neuromodulation approaches on improving stuttering treatment. Despite recent advancements in our understanding of the neurobiology of stuttering, *neuroscience-based treatments* for stuttering are limited. Techniques that exploit the principles of neuroplasticity, such as neuromodulation with transcranial direct current stimulation (tDCS), may offer new insight into effective stuttering treatment. This technique is safe, well-tolerated, and non-invasive (Bikson et al, 2016) compared to other stimulation techniques like transcranial magnetic stimulation (TMS). Additionally, tDCS readily lends itself to double-blinded, sham-controlled studies suitable for *randomized clinical trials* (Woods et al., 2016). Conventional tDCS sponge electrodes are large (e.g., 35 cm^2), resulting in diffuse current spread, but focality has recently been improved with high definition (HD) electrodes, which will be used in the proposed research (Datta et al., 2008; 2009; Kuo et al., 2013). Stimulation can increase or decrease brain activity using a weak constant electrical current (1-2mA). Unlike TMS, which can induce neural firing, tDCS affects resting membrane potential through the modulation of cellular-level changes, including sodium and calcium-dependent channels and NMDA receptor activity, promoting long-term potentiation/depression (LTP/LTD) like effects (Bolognini et al., 2011; Fritsch et al., 2010; Stagg et al., 2011). Previous findings suggest this is especially true when stimulation is delivered over multiple rather than single sessions (Woods et al., 2016), as will be done in the proposed intensive training program.

Both cognitive and motor rehabilitation fields have benefitted from the *translational nature of tDCS.* It can introduce functional improvement in language and motor skill learning (Cappon et al., 2016; Hashemirada et al., 2016; Hartwigsen, 2015; Madhavan & Shah, 2012; Reis et al., 2009). Applying tDCS during motor training can induce short- and long-term (up to 3 months) effects on rehabilitation after stroke (Allman et al., 2016; Reis et al., 2009). Further, (HD)-tDCS improves performance in unimpaired speakers, and speakers with aphasia, on such tasks as verbal fluency, speech reaction time, naming, numerical processing, spelling, and learning an artificial grammar (Baker et al., 2010; Cattaneo et al. 2011; De Vries et al., 2010; Dockery et al., 2009; Fertonani et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011; Iyer et al., 2005; Malyutina & Den Ouden, 2015; Richardson et al., 2015; Sparing et al., 2008; Vestito et al., 2014).

Another approach is to use tDCS in conjunction with functional magnetic resonance imaging (fMRI) to examine brain function before and after stimulation (Baudewig et al., 2001; Hampstead et al., 2014; Jang et al., 2009; Keeser et al., 2011; Polanía et al., 2012b; Stagg et al., 2009). Stimulation not only affects cortical areas immediately under the electrode(s), but also anatomically and functionally connected cortical (Holland et al., 2016; Pereira et al., 2013) and subcortical (Polania et al., 2012a; Lang et al., 2005; Liew et al., 2014; Weber et al., 2014). Such findings are important precedents for the proposed project. By stimulating left pSTG during choral speech, we aim to increase functional connectivity within BGTC regions through cellular-level changes that underlie LTP effects supporting long-term fluency.

2.4. Summary of significance

Accumulating evidence supports the effectiveness of neuromodulation approaches in treating speech-language disorders, and converging evidence points to specific brain regions (e.g., pSTG) that may be targeted to increase fluency in stuttering speakers. The current proposal aims to determine whether neuromodulation targeting the left pSTG can contribute specifically to increases in speech fluency of AWS and/or changes in brain functional connectivity in a network of regions supporting internal timing of speech (i.e., the BGTC). Presently, there is evidence that when compared to fluent controls, people who stutter exhibit difficulties relevant to generating internal timing that supports speech motor control, difficulties that appear related to abnormalities within the BGTC. The proposed project is *significant* because it has the potential to lead to neuroscience-based treatments that may have longer-lasting positive outcomes, reducing negative impacts on the lives of people who stutter. The objective of the proposed project is to establish the degree to which traditional fluency-inducing techniques can be augmented through targeted stimulation of relevant brain areas. Such efforts must precede testing of any other

more practical, generalizable behavioral technique to be paired with (HD)-tDCS in treating stuttering.

3. Method

3.1. Subject Recruitment and Screening

Participants will be recruited through community advertisements such as UMHSClinicalStudies.org or Craigslist, in the hospital, community, local papers; word of mouth; letters to area clinicians; stuttering support groups; through the National Stuttering Association website; and on lab websites and Facebook pages (www.neurostutteringresearch.com, www.facebook.com/msudevelopmentalstutteringproject/). We also will post infrequently in other relevant Facebook groups. All potential participants who contact the study coordinator will be briefed on the study and screened to ensure eligibility criteria are met. If the criteria are met, a face-to-face interview will be arranged, during which the written consent form will be completed, and the full assessment will occur. Information about the study may also be exchanged via email but participants will be discouraged from communication any personal information via the email system. Participants will be contacted up to 3 times if no response is received following their initial contact with the research team.

General participant criteria. The following criteria must be met by all participants:

- Between the ages of 18 and 65 years
- A history of persistent developmental stuttering,
- Stuttering severity ranging from mild to very severe, specifically Stuttering Severity Instrument (SSI) total score of 20 or higher and/or stuttering rates of 3% or higher,
- Not received any treatment for stuttering within the past year,
- No other neurological conditions such as Tourette's syndrome or post-traumatic stress disorder,
- Not taking any medications/drugs that affect brain function.
- No history of serious medical or neurological illness such as epilepsy and Parkinson's disease,
- No history of closed head injury (e.g., concussion),
- No history of reading disorders,
- No hearing loss,
- Not taking any medication, prescription or non-prescription with any psychotropic effects at the time of the study,
- No metal or electronic implants such as cochlear implants, and pacemakers,
- Scores within 1SD of the norm on the standardized tests for the study.

3.2. *Assessment.* Prior to assessment, the study will be explained to participants and an informed consent document signed. The assessment will consist of 3 parts: 1) Interview (review of medical history and history of stuttering), 2) standardized tests, and 3) speech sample collection.

3.3. *Interview.* Participants will be interviewed to obtain information on their medical and general speech history, as well as family history of stuttering, stuttering onset, and development. We will also ask questions about their musical training experience.

3.4. *Standardized assessments.* The standardized tests will provide measures of expressive and receptive language/vocabulary, speech fluency/stuttering severity, and working memory. The assessments may consist of the following:

- The Peabody Picture Vocabulary Test (PPVT-3; Dunn & Dunn, 1997)
- Expressive Vocabulary Test (EVT-3; Williams, 1997)
- Overall Assessment of the Speaker's Experience of Stuttering (Yaruss & Quesal, 2010)
- Operation span (Unsworth, Heitz, Schrock, & Engle, 2005)

3.5. *Speech samples.* Speech samples will consist of a reading task and a conversation between the participant and researcher. The reading and conversation will be audio- and video-taped. Speech samples will be transcribed off-

line and analyzed for disfluencies and any unusual speech-language usage. The severity of stuttering will be based on the reading and conversation speech samples collected. The Stuttering Severity Instrument (SSI-4) (Riley, 2009), will be used to assess the severity of stuttering during these samples. Two trained speech pathologists or research investigators experienced in disfluency analysis will independently score the SSI form to establish reliability of measurement. To be identified as a person who stutters, the overall SSI score is required to be 20 (corresponding to mild stuttering severity) or greater. Additionally, participants will be asked to rate their speech (e.g., very fluent, disfluent) and stuttering (e.g., mild, severe) within and outside the research setting.

3.6. Experimental design

Participation will require 10 separate visits.

- Visit 1 will consist of the interview, speech/language assessments, and a baseline speech sample (~ 1.5 hours).
- Visit 2 will consist of a second baseline speech sample and behavioral testing (~ 2 hours).
- Visit 3 will consist of a third baseline speech sample, MRI, and the first tDCS session (~2 hours).
- Visits 4, 5, 6 will consist of tDCS sessions (~1 hour each; 3 hours total)
- Visit 7 will consist of the final tDCS session, MRI, and behavioral testing (~3.5 hours)
- Visits 8-9 will consist of the second and third post-testing speech sample (~15 minutes each; 30 minutes total)
- Visit 10 will be 1 month (~4 weeks) after visit 7 and will consist of a final speech sample, MRI, and behavioral testing (~3.5 hours)

Visits 3 through 7 must be completed on consecutive days. Participants will also be sent a short online survey about their experiences with the tDCS procedure about 2 days after each visit; this survey will take no more than 5 minutes to complete. The potential amount of time needed for the entire study will be approximately 15-17 hours.

This project employs a between-subjects, sham-controlled, double-blinded design. Participants will be randomly assigned to either active or sham stimulation conditions. Total study time will be 2 weeks, plus a follow up appointment 4 weeks after training ends. Three speech samples (SS) will be collected during the first 1-2 weeks prior to training to obtain average baseline measures of speech fluency. Speech-language (SL) testing and collection of the first speech sample will be during the first visit. Visit 2 will consist of the second baseline speech measure and baseline measures of behavioral performance on the rhythm judgment tasks. On the third baseline visit, designated as Time 1 for analyses in sections 2 and 3 below, pre-training fMRI scans will be acquired and the first HD-tDCS session will be completed. Visits 4-6 will consist of tDCS sessions only. Visit 7 will consist of the final tDCS session, post-training MRI, and post-training behavioral testing and speech sample. Within the next 1-2 weeks, two speech samples (visits 8, 9) will be collected. Visit 10 will be 4 weeks after visit 7 and will consist of the final speech sample, fMRI, and behavioral testing.

3.7. Rhythm judgment and tapping tasks

Participants will compete tests of rhythm perception and judgment, including finger tapping and beat similarity judgments. These tasks will be completed on a computer or iPad and will take between approximately 2 hours to complete. Participants will be seated in a comfortable chair in a quiet room during testing.

3.8. HD-tDCS protocol

Stimulation parameters and target location. Stimulation will be delivered using a Soterix 4x1 HD-tDCS adapter with the 1×1 tDCS for Clinical Trials system. Modeling software (HD-Explore™, Soterix Medical Inc.) will be used to determine the best electrode montage to optimize targeting of left pSTG. The 4 (cathode) x 1 (anode) montage produces reliable changes in the electric field, and limits the stimulation area to within the area

circumscribed by the montage. A current of 2mA was selected because it is well-tolerated, safe, and effective (Bikson et al., 2016; Woods et al., 2016).

Procedure and tasks. During each session of the training period, stimulation (active or sham) will be delivered 20 minutes daily for 5 consecutive days. In both active and sham conditions current is automatically ramped up over 30 seconds. In the sham condition current is ramped down to zero for the remainder of the time to avoid stimulation of the brain. During stimulation, participants will engage in choral speech by reading overtly with a recording of the same text at a comfortable rate. Text will be at a 5th grade level and sufficient in length such that repetition of text will not occur during training.

3.9. fMRI protocol

Procedure. All participants will be scanned to assess brain activation within the speech motor control network. Procedures will be identical and scan time will be about 1 hour at each time point. All fMRI scans will be acquired at the University of Michigan fMRI laboratory using a 3T GE MRI scanner (MR 750). A standard echoplanar pulse sequence will be used. High-resolution structural images will be acquired at the beginning of each session using spoiled gradient-recalled acquisition in steady state (SPGR) imaging. Recent advancements in de-noising methods by Dr. Chow and colleagues (Xu et al., 2014) allow us to collect fMRI data during continuous, narrative speech providing a more natural speaking condition than is typically used in task-based fMRI studies. Speech in the scanner will be recorded with an optical noise cancellation microphone and an MR-compatible camera mounted on the scanner head-coil. Resting state fMRI will also be acquired.

Stimuli and tasks. During the functional scanning, participants will complete continuous speech production tasks.

3.10. Data analysis

Primary Outcome Measure 1- Changes in brain activation as assessed by fMRI images

Functional images will be de-noised using spatial Independent Component Analysis (sICA), a signal un-mixing algorithm to separate speech and movement artifacts (Xu et al., 2014). This method has been validated against PET studies (Xu et al., 2014) and used to study continuous speech production (AbdulSabur et al., 2014). Task-based and functional connectivity analysis will be conducted using the conditions which contained continuous speech. We expect the magnitude of change to be greater in the active group than in training alone (sham tDCS). The functional connectivity analyses will be conducted on both task-based and resting state data.

Primary Outcome Measure 2 - Change in percentage of stuttered syllables produced during speech sample (speech fluency)

To measure effects of tDCS on fluency we will calculate %SLD at each of the 3 time points. Two speech pathologists trained in disfluency analysis and blinded to group assignment and time point will independently score %SLD to establish reliability. The outcome measure is the difference between baseline measures of (mean) %SLD and the same measure at 2 post-training time points. While an increase is expected to occur in both groups, we expect that the magnitude of any differences will be greater in the group receiving active stimulation compared to training alone (sham stimulation). We expect that: 1) %SLD will decrease significantly more in the active stimulation group compared to the sham group, and 2) these differences will be maintained when assessed 4 weeks later.

Secondary Outcome Measure 1 - Changes from baseline on the Overall Assessment of Speakers Experience of Stuttering (OASES)

The OASES is a standardized assessment of the functional impact of stuttering on a person's life. There are 4 sub-tests: general information about speech, your reactions to stuttering, communication in daily situations, quality of life. Each one has a score from 1 to 5 with regard to impact (1 least, 5 most negative impact). These are combined to give a total impact score between 1 and 5, with 5 representing the highest negative impact on person's life. The change on the total impact score will be used.

Other (Exploratory) Outcome Measures

1. Changes from baseline on rhythm judgement task

Investigators will compare performance accuracy on a computerized rhythm judgement task from before and after tDCS to assess effects of tDCS. Improved accuracy reflects better performance.

2. Changes from baseline on tapping tasks
Investigators will compare performance (variability and accuracy) on computerized tapping tasks from before and after tDCS to assess effects of tDCS. Decreased variability and improved accuracy reflect better performance.

3. Changes from baseline on self-rated measure of speech fluency
Investigators will compare participant scores on a self-rated measure of speech fluency (1 = NO STUTTERING; 9 = EXTREMELY SEVERE STUTTERING) from before and after tDCS to assess effects of tDCS. Lower scores indicate improvement.

4. Protection of Human Subjects

4.1. Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design
The proposed study will involve healthy adult participants between 18-65 years of age. All participants in the tDCS arm will be those who have been diagnosed with developmental stuttering. Although women are underrepresented in samples of adults with stuttering, we will make every effort to include women in the proportion they occur in the population with this disorder. While the ratio is closer in childhood, approximately 3 males to 1 female, in adults the ratio is approximately 5 males to 1 female. We will gather information on each participant's medical, social, and developmental history, and speech, language, and hearing background. In addition, stuttering participants will be audio-video recorded to obtain speech samples during conversation and reading. These will be used to determine their stuttering severity level using the standardized assessment, stuttering severity instrument (SSI-4; Riley 2009). Two trained speech-language pathologists experienced in disfluency analysis will independently score the SSI form to establish reliability of measurement. Participants will be randomly assigned to one of the two groups (active vs. sham stimulation).

In order to reach our target of 24 eligible adults who stutter who complete the study, and 50 eligible controls to participate in the rhythm tasks sub study only (see section 4.5 below), we will consent up to 200 people during the oral phone screening. It is possible that some participants who pass this screening may still become ineligible during the first visit, for example due to scoring below normal on the standardized tests, or having a stuttering score that is too low.

Sources of Materials.
This project involves ***four sources*** of research material: (1) ***Questionnaire data*** (e.g., Intake screening form, developmental history, demographic information, etc.), (2) ***Brain imaging data*** (e.g., high resolution structural image (MPRAGE), functional MRI), (3) ***Audio-video recorded data*** (e.g., audio-videotaping in a laboratory setting to sample speech), and (4) ***Behaviorally coded data*** (e.g., during testing, some behavioral observations will be coded by either paper-and-pencil means and/or subsequently through the use of computerized software e.g., frequency of stuttering-like disfluencies per task and/or during conversation, hearing screening data). All such data, whether in DVD, video, or paper format, will be stored in a locked filing cabinet in a locked storage room in the Rachel Upjohn Building at the U of M East medical campus, accessible only to the applicant and her mentorship team, and their students and staff. Once computerized data have been coded, organized and statistically analyzed, they will be stored in a password-protected computer housed in Dr. Chang's lab. All computerized data files will contain only participants' non-identifying code numbers.

4.2. Potential Risks.

Breach of privacy. The risks involving breach of sensitive private information will be minimized by having all participants' data de-identified and handled only by Dr. Garnett and other authorized investigators. All subject data will be placed in individual coded files that will be locked in a cabinet in Dr. Garnett's office or lab.
Inconvenience or discomfort during behavioral testing. All participants will be given breaks as needed, and will not be pressured to continue if there is excessive anxiety or fatigue.

Inconvenience or discomfort during HD-tDCS. Any level of discomfort will be monitored very closely by an investigator that will be sitting beside the participants at all times during the experiment. If discomfort is noticeable/bothersome, we will discontinue the procedures immediately. In our experience (combined at UM and Dr. Garnett's doctoral research institution) we had no participants expressing discomfort that required termination of the study. Most complaints, if any, involved a "tingling", "itchy" sensation, rather than pain. There is only a minor risk of discomfort with HD-tDCS. Some people have reported slight itching or tingling sensation below the electrodes with HD-tDCS. A less common side effect is temporary skin redness and mild headache. Although adverse side effects such as seizures are possible, the procedure has been used safely without any reports of such adverse effects. Increased risk of skin burns and infection as a result of a single session of stimulation using conventional tDCS has been reported (Wang, Wei, Wen, & Li, 2014). However, in our study we will be using HD-tDCS rather than conventional tDCS. To date, there have been no reports of burns with high definition tDCS (Brunoni et al., 2011; Brunoni et al., 2012) and participants will be closely monitored throughout the study. If participants have a skin injury such as cuts or scrapes on their skin before participating in the study, they will not be eligible to participate as it will increase the likelihood of skin irritation. Additionally, headaches during and after stimulation may occur. It is unknown if HD-tDCS can pose a risk to fetuses. Also, to minimize other potential risks of tDCS, we will ask that participants fill out a side effects questionnaire after the stimulation. On the questionnaire, there will be a list of potential symptoms participants may experience. Participants are to check a box that best describes the symptom(s) they may be experiencing. The description of the symptoms range from Absent to Severe. Participants will also be asked to best describe the relationship between HD- tDCS and their symptoms. For a recently published comprehensive review of safety related to tDCS, please refer to Bikson et al. (2016).

The researchers will try to minimize these risks. We will be monitoring the subjects closely during the procedure. For all studies, we will use saline electrode gel to minimize the itching experienced. We will also slowly ramp up the current to the desired, low stimulation intensity. We will not exceed the stimulation intensities (2 mA) and durations (maximum of 20 min) that are known to be safe and closely monitor the condition of the skin throughout each session. We will monitor the condition of the skin to avoid significant discomfort. We will also ask the subjects questions about the subject's medical history to ensure the subject do not have any additional risk factors (e.g., a history of epilepsy) for a seizure prior to participating in this study. For women, the subject will be asked during screening whether she is pregnant or are trying to become pregnant; they should not take part in this study if they are. Sexually-active women of child-bearing potential are asked to use a reliable birth control method for the duration of this study. Also, to minimize other potential risks of tDCS, we will ask that the subject fill out a side effects questionnaire after the tDCS stimulation. On the questionnaire, there will be a list of potential symptoms the subject may experience. They are to check a box that best describes the symptom(s) They may be experiencing. The description of the symptoms range from Absent to Severe. They will also be asked to best describe the relationship between tDCS and the symptoms.

Inconvenience or discomfort during MRI scanning. Well-known risks for MRI scanning involve the presence of ferromagnetic foreign objects in and/or on the body (e.g., pacemaker, surgical clip, staples, etc.), claustrophobia, as well as possible inconvenience or discomfort during the scanning due to the requirement of lying still, and exposure to loud noise. The risks involved in MRI participation are usually greatly minimized through a thorough screening procedure performed by Dr. Garnett as well as the fMRI Research Lab staff, followed by ample opportunity for exposure to the sights and sounds of the MRI setting, as well as the option to participate in a desensitization session in a mock MRI. Discomfort due to loud noise during scanning will be minimized through use of earplugs, headphones, and padding around the head as well as the inside of the MRI bore. If a participant shows any signs of discomfort or anxiety during the scanning, the procedure will be interrupted and stopped if necessary.
There is a minor risk of discomfort or anxiety from being in the confined space of the MRI scanner. The MRI scanner makes loud, vibrating noises. Some studies, like this one, have the potential to cause "peripheral nerve stimulation" (PNS). PNS is a light touching sensation on the skin surface, lasting only for a few seconds. There is also a risk that the magnetic fields could disturb a metal fragment in the body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in the

body to heat up, causing the subject harm. Sometimes, subjects report a temporary, slight dizziness, light-headedness or nausea during or immediately after the scanning session.

To minimize these risks and discomfort, we will provide pads and blankets to make the subject as comfortable as possible. The subject will be able to talk to us throughout the study, and will be able let us know right away if they want to stop the study and get out of the scanner. They will wear foam earplugs to reduce the loud noises made by the scanner and prevent any hearing damage. It may cause mild discomfort, but is not harmful to them. The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low. If they feel dizzy or light-headed, we will have them get up slowly from the scanner. Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside the body could be accelerated by the magnetic field and strike them, causing them injury. We keep the environment around the MRI scanner completely free of loose metal objects that could be moved by the magnetic field, and we will make sure that they have no metal on the body that could be affected by the MRI scanner.

We will also ask them questions and have them complete an MRI screening form to make sure that they have no metal inside the body that would cause them harm during the MRI scan.

Further, they will not be enrolled in the study if they: 1) have a heart pacemaker, 2) are pregnant, 3) have had brain surgery for an aneurysm (weakening of the blood vessels), 4) have had major surgery within the past 4 weeks, 5) have a neurostimulator (a device that sends precise electrical pulses to the stomach), 6) have metal fragments in or near the eye or brain, or 7) are claustrophobic (fear of being in closed spaces).

As with any research study, there may be additional risks that are unknown or unexpected.

Incidental MRI and/or behavioral findings. Any MRI scans that appear to have potential clinical abnormality will be forwarded to a neuroradiologist, and if confirmed abnormal, the findings will be communicated to the study investigator, who would notify the participant and, with permission, be forwarded to the participant's primary care physician. Further referrals to appropriate clinicians would be made as appropriate.

4.3. Adequacy of Protection Against Risks

Recruitment and Informed Consent

Recruitment. Participants will be recruited through community advertisements such as in the hospital, community, local papers; word of mouth; letters to area clinicians; stuttering support groups; through the National Stuttering Association website; and on lab websites and Facebook pages http://neurostutteringresearch.com, https://www.facebook.com/msudevelopmentalstutteringproject/

All potential participants who contact the team will be briefed on the study and screened to ensure eligibility criteria are met. If the criteria are met, a face-to-face interview will be arranged, during which the written consent form will be completed, and the full assessment will occur. Information about the study may also be exchanged via email but participants will be discouraged from communication any personal information via the email system. Participants will be contacted up to 3 times if no response is received following their initial contact with the research team.

Informed consent. The PI will first provide an overview of what is involved in the study participation, explain risks and benefits of participating, and that participation is voluntary, and that they may stop participation at any time without penalty. Then the investigator will encourage participants to read over the consent form carefully and to ask any questions before signing the form. A copy of the consent form will be given to the participant for their records. Also, when necessary, the PI or study coordinator will read the consent form to the participant and verbally provide information about the study; and verbal consent from the participant will be recorded in the researchers' note and/or recorded on a digital/audio recorder.

4.4. Protection Against Risk.

Risks in participating in standardized testing, hearing screening, videotaping of speech, tDCS, and MRI imaging and so forth are minimal. To minimize risks, we will, before each assessment begins (as explained above), thoroughly explain all procedures to each participant. Also, as suggested above, ample time will be allowed, for participants to ask questions about procedures, study goals, and methods. Written consent forms, that have first

been verbally described, will be presented to the participants for their review and signature. At any time during any assessment, the participant will have the opportunity to end the session without penalty. Participants will be reimbursed for their participation, effort, time, and travel to assist them with costs and inconvenience to their schedules. Resulting test scores, performance during experimental testing, etc. associated with each participant will be, as discussed above, stored in the PI's laboratory in the Rachel Upjohn Building. Once data has been coded, organized and statistically analyzed, it will be stored in a computer housed in the PI's lab in data files containing only participants' de-identified code numbers. All data will be assigned a subject code, and only the PI and active study investigators will have access to the linking information that connects subject ID to study code. All subject data will be kept in locked cabinets within locked offices at the Rachel Upjohn Building. The consent form, questionnaires and all testing will take place in a restricted use room. Participants will complete the questionnaires in an area where their responses cannot be seen or heard by others not directly participating in the study.
For women of child-bearing potential. To minimize this risk, participants are asked during their screening whether they are pregnant or are trying to become pregnant, and are not enrolled in the study if they are. Sexually-active women of child-bearing potential will be asked to use a reliable birth control method for the duration of this study.

4.5. Separate sub study for healthy controls only

We will also recruit approximately 50 adults who do not stutter to participate in a sub study to examine the effects of repeated training on the rhythm tasks (section 3.7). We need people who do not stutter to complete these tasks to get more information about the tasks. To get this information, we'd like 50 people between the ages of 18-65 years who do not stutter to perform the same tasks. This will be done on a computer and/or iPad. These tasks will involve listening to rhythms and making judgments about them, as well as performing some finger tapping exercises. Participants will complete these tasks 3 times: 1) the initial visit, 2) 5 days later, and 3) 4 weeks after visit 2. During their first visit, we may also administer brief speech and language tests, which involve looking at some pictures and answering questions about them, and a short working memory test. We will also ask them about musical training history. Therefore, the first visit will take approximately 2 hours, and visits 2 and 3 will take approximately 1 hour. These participants will only complete the speech assessment, musical training history, operation span, and rhythm tasks. They will not receive HD-tDCS or an MRI. They will complete the rhythm tasks three times: 1) initial visit, 2) 5 days later, and 3) 4 weeks after visit 2. This is to mimic the testing procedure of the adults who stutter.

The only exclusion criteria would be history of stuttering or other speech, language, memory, cognitive, or psychiatric disorders.

These subjects will receive $50 for participating in this study via check in the mail. Additionally, if they complete the 1 month follow up (visit 3), they will receive a $25 bonus.

They will sign a separate consent form. To keep their information confidential, we will label the survey and tests with a code, rather than their name or any other details that someone could use to identify them. Although we'll keep a list of all the people who answered our survey, no one outside our study team will be able to figure out who answered the survey or which people gave which answers. Completion of these tests won't benefit them directly. We hope what we learn will help other people in the future. The only risks include mild discomfort involved in completing the tests.

4.6. Data Safety Monitoring Plan

Study Title: Non-invasive brain stimulation in adults who stutter
Principal Investigator: Emily O. Garnett, Ph.D., CCC-SLP
Mentors: Soo-Eun Chang, Ph.D., CCC-SLP and Benjamin Hampstead, Ph.D.

BRIEF STUDY OVERVIEW

The first goal of this project is to determine the benefits of applying high-definition transcranial direct current stimulation to targeted brain regions during a brief, intensive fluency training program on speech fluency in adults

who stutter. The second goal of this project is to determine stimulation effects on functional connectivity in brain networks involved in the timing and rhythm aspects of speech motor control in adults who stutter.

OVERSIGHT RESPONSIBILITIES

Oversight of the trial is provided by the Principal Investigator (PI), Dr. Garnett and her mentors, Dr. Soo-Eun Chang and Dr. Benjamin Hampstead.

MONITORING PROCEDURES

The study team will conduct scheduled assessments of study recruitment, data integrity and quality, adverse events, withdrawals, and compliance with protocol plan monthly. No additional monitoring is required – the nature, size, and complexity of this study does not require additional safety monitoring to that provided by the IRB.

COLLECTION AND REPORTING OF SAEs AND AEs

Adverse event: AEs involve physiological, social, economic, or psychological harm to subjects. These adverse events may also indicate risks of harm to additional subjects or others. AEs include expected and unexpected harmful effects, and unexpected harms of an interaction or an intervention. AEs are identified by: direct interviews/ physical exams conducted; review of lab work, tests, procedures, etc., telephone follow-up conducted; self-reporting by subject

Serious Adverse Event:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

AEs are graded according to the following scale:

0 - No adverse event
1 - Mild AE – No treatment needed
2 - Moderate AE – Resolved with treatment
3 - Severe AE – Inability to carry on normal activities, required professional medical attention
4 - Life-threatening or disabling AE
5 - Fatal AE

The study uses the following AE attribution scale as defined by the IRB:

EVENTS RELATED

Definitely Related

- The event is a known effect of the drug, device, or procedure (e.g., listed in the protocol documents including IB, consent, publications)
- The event follows an obvious sequence of time, from the drug's administration, device's implantation or activation, or procedure, for which the event is directly attributed to the administration, implantation, activation, or procedure.
- The event ceases with discontinuation of the drug, device, or procedure (and reoccurs on restarting).
- The event includes data that was only collected for the study.
- The event included disturbing or upsetting questions that the subject was asked for the purpose of the research.

Probably Related

- The event is lesser known or suspected effect of the drug, device, or procedure (listed in the protocol documents including IB, consent, publications, etc.)
- The event follows a reasonable sequence of time from the drug's administration, device implantation, activation, or procedure, for which the event may be attributed to the administration, implantation, activation, or procedure.
- The event ceases or diminishes with discontinuation of the drug, removal/discontinued activation of the device, or procedure.

Possibly Related

- The event is a lesser known or possible effect of the drug, device, or procedure.
- The event occurred within a sequence of time from the drug's administration, device implantation and/or activation, or procedure, for which the event may be attributed to the administration, implantation, activation, or procedure.
- The event could be explained by the characteristics of the population under study.

EVENTS NOT RELATED

Unlikely Related

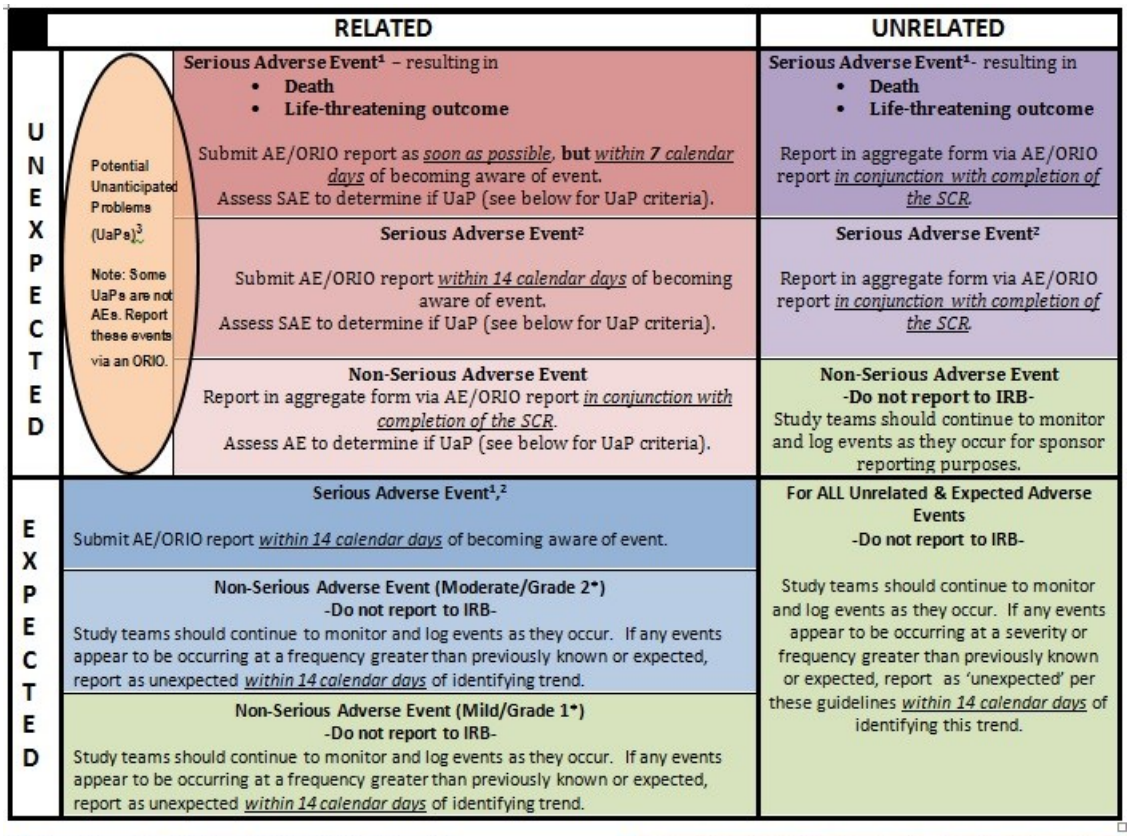
- The event is NOT a previously known or suspected effect of the test drug, device, or procedure.
- The event does NOT follow a sequence of time from drug administration, device implantation and/or activation, or procedure, for which the event could be attributed to the administration, implantation, activation, or procedure.
- The event can be readily explained by the characteristics of the population under study.

Unrelated

- The event is NOT known to be an effect of the test drug, device, or procedure.
- The event does NOT follow a sequence of time from drug administration, device implantation and/or activation, or procedure, for which the event could be attributed to the administration, implantation, activation, or procedure.
- The event can be readily and easily explained by the characteristics of the population under study.
- Subject never received study drug, study device, or underwent research study procedure.

EXPECTEDNESS will be assigned for each adverse event according to the following definitions:

- *Unexpected adverse events* (i.e., has NOT been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation)
- *Expected adverse events* (i.e., has been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation, or characteristics of the study population)



	RELATED	UNRELATED
UNEXPECTED	Potential Unanticipated Problems (UaPs)[3] Note: Some UaPs are not AEs. Report these events via an ORIO.	
	Serious Adverse Event[1] – resulting in • **Death** • **Life-threatening outcome** Submit AE/ORIO report as *soon as possible*, **but** *within 7 calendar days* of becoming aware of event. Assess SAE to determine if UaP (see below for UaP criteria).	**Serious Adverse Event[1]**- resulting in • **Death** • **Life-threatening outcome** Report in aggregate form via AE/ORIO report *in conjunction with completion of the SCR*.
	Serious Adverse Event[2] Submit AE/ORIO report *within 14 calendar days* of becoming aware of event. Assess SAE to determine if UaP (see below for UaP criteria).	**Serious Adverse Event[2]** Report in aggregate form via AE/ORIO report *in conjunction with completion of the SCR*.
	Non-Serious Adverse Event Report in aggregate form via AE/ORIO report *in conjunction with completion of the SCR*. Assess AE to determine if UaP (see below for UaP criteria).	**Non-Serious Adverse Event -Do not report to IRB-** Study teams should continue to monitor and log events as they occur for sponsor reporting purposes.
EXPECTED	**Serious Adverse Event[1,2]** Submit AE/ORIO report *within 14 calendar days* of becoming aware of event.	**For ALL Unrelated & Expected Adverse Events -Do not report to IRB-** Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a severity or frequency greater than previously known or expected, report as 'unexpected' per these guidelines *within 14 calendar days* of identifying this trend.
	Non-Serious Adverse Event (Moderate/Grade 2*) -Do not report to IRB- Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a frequency greater than previously known or expected, report as unexpected *within 14 calendar days* of identifying trend.	
	Non-Serious Adverse Event (Mild/Grade 1*) -Do not report to IRB- Study teams should continue to monitor and log events as they occur. If any events appear to be occurring at a frequency greater than previously known or expected, report as unexpected *within 14 calendar days* of identifying trend.	

[1]Serious Adverse Event (SAE) as reflected in (32-1.4 in eResearch)	[3]Potential Unanticipated Problems Involving Risks to Subjects or Others (UaP)
• Death • A life-threatening adverse drug/device experience or outcome	1) Is the event **unexpected** in nature, frequency, or severity? 2) Is the event **related** to the research? 3) Is there an **increased risk** of potential harm and/or actual harm than was previously known or recognized? • If yes to **all three**, this is a potential UaP. Include "Potential UaP" in description of event when reporting. • If no to any, *this is **not** a potential UaP*. Report as described above.
[2]Serious Adverse Event (SAE) as reflected in (32-1.4 in eResearch)	**University of Michigan UaP Reporting**
• Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant disability/incapacity or permanent damage • A congenital anomaly or birth defect • Other serious important medical events • Based on medical judgment AND may require medical or surgical intervention to prevent one of the above	UaPs that are also SAEs should be reported to the IRB according to the AE reporting guidelines detailed in this document. UaPs that are NOT SAEs (e.g., ORIO, AEs) should be reported to the IRB within 14 calendar days of becoming aware of event.
EXTERNAL Site Adverse Event Reporting Do not report External Adverse Events to the IRB, unless they have been determined by the external site PI to be a UaP. See Statement of Practice here.	**EXTERNAL Site UaP Reporting**: Submit External site UaPs *within 14 calendar days* of becoming aware of event.

This chart is for studies following IRBMED standard AE reporting. This is provided as a general guideline/explanation of the reporting process at UM.

5. Training of all individuals who administer tDCS

5.1. All personnel involved in tDCS sessions will be familiar with the safety guidelines and with the seizure protocol. A seizure protocol will be posted in a visible location in the room where tDCS will be delivered. The seizure protocol is as follows:

In the event of a seizure

Protect from injury: Tilt chair back to flatten. Protect head and body from injury using padding. Move any objects out of range that could potentially cause injury. Place a small folded blanket or other cushioning under the head if it is moving violently. Loosen any zips/ buttons close to the neck (e.g., jackets). If possible, turn subject on his/her side to prevent aspiration.

ABC's: (airway, breathing, circulation): Maintain a clear airway (head tilt, chin lift). Assess cardiorespiratory function (breathing and pulse).

Activate EMS (Emergency Medical Services): Call Huron Valley Ambulance – 994-4111. If breathing and pulse are present, state, "Medical emergency at [location, building name and number]." If breathing and/or pulse are absent, state, "Cardiac arrest at [location, building name and number]".
Record time and duration of seizure. Do not: restrict movement, insert of force objects into the mouth.
After the seizure: Maintain a clear airway: Subject to rest on his/her side to prevent aspiration. Help to reorient the subject: provide reassurance. Remain with the subject 1:1 until fully oriented and stable. Check vital signs. Have the subject transported to the Emergency Department for assessment.
Documentation: When the subject is stabilized, document the following: Incident preceding the seizure (stimulation parameters, duration of stimulation). Description of seizure (parts of the body involved in the seizure, types of movement, time and duration of seizure). Medical personnel notified and time. Treatment given or emergency measures taken. Any injury incurred during the seizure. Subject's clinical status post-seizure.

References

Alm, P. A. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of communication disorders, 37*(4), 325-369.

Antal, A., Polania, R., Schmidt-Samoa, C., Dechent, P., & Paulus, W. (2011). Transcranial direct current stimulation over the primary motor cortex during fMRI. *Neuroimage, 55*(2), 590-596.

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *The international journal of neuropsychopharmacology, 11*(02), 249-254.

Bohland, J. W., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. *Journal of Cognitive Neuroscience, 22*(7), 1504-1529.

Bolognini, N., Vallar, G., Casati, C., Latif, L. A., El-Nazer, R., Williams, J., . . . Chessa, C. (2011). Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabilitation and neural repair, 25*(9), 819-829.

Borckardt, J. J., Bikson, M., Frohman, H., Reeves, S. T., Datta, A., Bansal, V., . . . George, M. S. (2012). A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. *The Journal of Pain, 13*(2), 112-120.

Borsel, J., Reunes, G., & Bergh, N. (2003). Delayed auditory feedback in the treatment of stuttering: clients as consumers. *International Journal of Language & Communication Disorders, 38*(2), 119-129.

Bothe, A. K., Davidow, J. H., Bramlett, R. E., & Ingham, R. J. (2006). Stuttering treatment research 1970–2005: I. Systematic review incorporating trial quality assessment of behavioral, cognitive, and related approaches. *American Journal of Speech-Language Pathology, 15*(4), 321-341.

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies. *Human brain mapping, 25*(1), 105-117.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Pascual-Leone, A. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation, 5*(3), 175-195.

Chang, S. E., Erickson, K. I., Ambrose, N. G., Hasegawa-Johnson, M. A., & Ludlow, C. L. (2008). Brain anatomy differences in childhood stuttering. *Neuroimage, 39*(3), 1333-1344.

Chang, S. E., Horwitz, B., Ostuni, J., Reynolds, R., & Ludlow, C. L. (2011). Evidence of left inferior Frontal–Premotor structural and functional connectivity deficits in adults who stutter. *Cerebral Cortex, 21*(11), 2507-2518.

Chang, S. E., Kenney, M. K., Loucks, T. M., & Ludlow, C. L. (2009). Brain activation abnormalities during speech and non-speech in stuttering speakers. *Neuroimage, 46*(1), 201-212.

Chang, S. E., & Zhu, D. C. (2013). Neural network connectivity differences in children who stutter. *Brain*, awt275.

Civier, O., Bullock, D., Max, L., & Guenther, F. H. (2011). *Dopamine excess may delay selection of syllabic motor programs: a Modeling study of stuttering.* Paper presented at the Proceedings of the 17th International Congress of Phonetic Sciences, Hong King, China.

Cuypers, K., Leenus, D. J., van den Berg, F. E., Nitsche, M. A., Thijs, H., Wenderoth, N., & Meesen, R. L. (2013). Is motor learning mediated by tDCS intensity? *PloS one, 8*(6), e67344.

DaSilva, A. F., Mendonca, M. E., Zaghi, S., Lopes, M., DosSantos, M. F., Spierings, E. L., . . . Fregni, F. (2012). tDCS-Induced Analgesia and Electrical Fields in Pain-Related Neural Networks in Chronic Migraine. *Headache: The Journal of Head and Face Pain, 52*(8), 1283-1295.

De Nil, L. F., Kroll, R. M., Lafaille, S. J., & Houle, S. (2004). A positron emission tomography study of short-and long-term treatment effects on functional brain activation in adults who stutter. *Journal of Fluency Disorders, 28*(4), 357-380.

Dunn, L., & Dunn, D. (1997). Peabody Picture Vocabulary Test. Circle Pines, MN: American Guidance Service. *Inc. Publishing*.

Etchell, A. C., Johnson, B. W., & Sowman, P. F. (2014). Behavioral and multimodal neuroimaging evidence for a deficit in brain timing networks in stuttering: a hypothesis and theory. *Frontiers in Human Neuroscience, 8*.

Fertonani, A., Rosini, S., Cotelli, M., Rossini, P. M., & Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behavioural brain research, 208*(2), 311-318.

Fox, P. T., Ingham, R. J., Ingham, J. C., Hirsch, T. B., Downs, J. H., Martin, C., . . . Lancaster, J. L. (1996). A PET study of the neural systems of stuttering.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron, 66*(2), 198-204.
Giraud, A.-L., Neumann, K., Bachoud-Levi, A.-C., von Gudenberg, A. W., Euler, H. A., Lanfermann, H., & Preibisch, C. (2008). Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. *Brain and language, 104*(2), 190-199.
Goldman, R., & Fristoe, M. (2000). Fristoe M. *Goldman-Fristoe test of articulation, 2*.
Grahn, J. A. (2009). The role of the basal ganglia in beat perception. *Annals of the New York Academy of Sciences, 1169*(1), 35-45.
Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and language, 96*(3), 280-301.
Hasan, A., Hamada, M., Nitsche, M. A., Ruge, D., Galea, J. M., Wobrock, T., & Rothwell, J. C. (2012). Direct-current-dependent shift of theta-burst-induced plasticity in the human motor cortex. *Experimental brain research, 217*(1), 15-23.
Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W.-H., Gerloff, C., & Cohen, L. G. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain, 128*(3), 490-499.
Iyer, M., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology, 64*(5), 872-875.
Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., . . . Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *The Journal of neuroscience, 31*(43), 15284-15293.
Kuo, H.-I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M.-F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study. *Brain stimulation, 6*(4), 644-648.
Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W., & Nitsche, M. A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clinical Neurophysiology, 120*(6), 1161-1167.
Lu, C., Peng, D., Chen, C., Ning, N., Ding, G., Li, K., . . . Lin, C. (2010). Altered effective connectivity and anomalous anatomy in the basal ganglia-thalamocortical circuit of stuttering speakers. *Cortex, 46*(1), 49-67.
Madhavan, S., & Shah, B. (2012). Enhancing motor skill learning with transcranial direct current stimulation–a concise review with applications to stroke. *Frontiers in psychiatry, 3*.
Maguire, G., Franklin, D., Vatakis, N. G., Morgenshtern, E., Denko, T., Yaruss, J. S., . . . Fox, P. (2010). Exploratory randomized clinical study of pagoclone in persistent developmental stuttering: the EXamining Pagoclone for peRsistent dEvelopmental Stuttering Study. *Journal of clinical psychopharmacology, 30*(1), 48-56.
Max, L., Guenther, F. H., Gracco, V. L., Ghosh, S. S., & Wallace, M. E. (2004). Unstable or insufficiently activated internal models and feedback-biased motor control as sources of dysfluency: A theoretical model of stuttering. *Contemporary issues in communication science and disorders, 31*, 105-122.
Neumann, K., Euler, H. A., Gudenberg, A. W. v., Giraud, A.-L., Lanfermann, H., Gall, V., & Preibisch, C. (2004). The nature and treatment of stuttering as revealed by fMRI: A within-and between-group comparison. *Journal of Fluency Disorders, 28*(4), 381-410.
Nitsche, M. A., Doemkes, S., Karakoese, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of neurophysiology, 97*(4), 3109-3117.
Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.
Orban, P., Peigneux, P., Lungu, O., Albouy, G., Breton, E., Laberenne, F., . . . Doyon, J. (2010). The multifaceted nature of the relationship between performance and brain activity in motor sequence learning. *Neuroimage, 49*(1), 694-702.
Packman, A., Code, C., & Onslow, M. (2007). On the cause of stuttering: Integrating theory with brain and behavioral research. *Journal of Neurolinguistics, 20*(5), 353-362.
Packman, A., & Onslow, M. (2002). Searching for the cause of stuttering. *The Lancet, 360*(9334), 655-656.
Packman, A., Onslow, M., Richard, F., & Van Doorn, J. (1996). Syllabic stress and variability: A model of stuttering. *Clinical linguistics & phonetics, 10*(3), 235-263.
Polanía, R., Paulus, W., & Nitsche, M. A. (2012a). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Human brain mapping, 33*(10), 2499-2508.

Polanía, R., Paulus, W., & Nitsche, M. A. (2012b). Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. *PloS one, 7*(1), e30971.
Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain research bulletin, 72*(4), 208-214.
Reis, J., Robertson, E. M., Krakauer, J. W., Rothwell, J., Marshall, L., Gerloff, C., . . . Celnik, P. A. (2008). Consensus: Can transcranial direct current stimulation and transcranial magnetic stimulation enhance motor learning and memory formation? *Brain stimulation, 1*(4), 363-369.
Riley, G. (2009). *Stuttering severity instrument for young children (SSI-4)*. Austin, TX: Pro-Ed. Inc.
Rodríguez, N., Opisso, E., Pascual-Leone, Á., & Soler, M. D. (2014). Skin lesions induced by transcranial direct current stimulation (tDCS). *Brain stimulation, 5*(7), 765-767.
Smith, A., Goffman, L., Sasisekaran, J., & Weber-Fox, C. (2012). Language and motor abilities of preschool children who stutter: Evidence from behavioral and kinematic indices of nonword repetition performance. *Journal of Fluency Disorders, 37*(4), 344-358.
Smith, A., Sadagopan, N., Walsh, B., & Weber-Fox, C. (2010). Increasing phonological complexity reveals heightened instability in inter-articulatory coordination in adults who stutter. *Journal of Fluency Disorders, 35*(1), 1-18.
Smits-Bandstra, S., & De Nil, L. (2009). Speech skill learning of persons who stutter and fluent speakers under single and dual task conditions. *Clinical linguistics & phonetics, 23*(1), 38-57.
Smits-Bandstra, S., & De Nil, L. F. (2007). Sequence skill learning in persons who stutter: implications for cortico-striato-thalamo-cortical dysfunction. *Journal of Fluency Disorders, 32*(4), 251-278.
Sommer, M., Koch, M. A., Paulus, W., Weiller, C., & Büchel, C. (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *The Lancet, 360*(9330), 380-383.
Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17*(1), 37-53.
Stagg, C. J., O'Shea, J., Kincses, Z. T., Woolrich, M., Matthews, P. M., & Johansen-Berg, H. (2009). Modulation of movement-associated cortical activation by transcranial direct current stimulation. *European journal of neuroscience, 30*(7), 1412-1423.
Toyomura, A., Fujii, T., & Kuriki, S. (2011). Effect of external auditory pacing on the neural activity of stuttering speakers. *Neuroimage, 57*(4), 1507-1516.
Unsworth, Heitz, Schrock, & Engle (2005). An automated version of the operation span task. Behavior Research Methods, 37, 498-505.
Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. *Neuropsychologia, 48*(10), 2789-2810.
Wang, J., Wei, Y., Wen, J., & Li, X. (2014). Skin burn after single session of transcranial direct current stimulation (tDCS). *Brain stimulation*.
Watkins, K. E., Gadian, D. G., & Vargha-Khadem, F. (1999). Functional and structural brain abnormalities associated with a genetic disorder of speech and language. *American journal of human genetics, 65*(5), 1215.
Williams, K. T. (1997). Expressive Vocabulary Test Second Edition (EVT™ 2). *Journal of the American Academy of Child & Adolescent Psychiatry, 42*, 864-872.
Yairi, E., Ambrose, N. G., Paden, E. P., & Throneburg, R. N. (1996). Predictive factors of persistence and recovery: Pathways of childhood stuttering. *Journal of communication disorders, 29*(1), 51-77.