PROTOCOL COVER PAGE

Protocol Title	Combining cerebellar tDCS and constraint-induced language therapy in non-fluent aphasia: a novel approach to target discourse
Principal Investigator/Faculty Advisor	Name: Sharyl Samargia-Grivette
	Department: Communication Sciences and Disorders
	Telephone Number: 218-726-8347
	Email Address: samargia@d.umn.edu
Student Investigator	Name: Madelyn Graham, Haley Evans, and Marie Meyesmbourg
	Current Academic Status (Student, Fellow, Resident): Graduate Students
	Department: Communication Sciences and Disorders
	Telephone Number:218-726-8347
	Institutional Email Address:evan0574@d.umn.edu, graha745@d.umn.edu, and meyse016@d.umn.edu
Scientific Assessment	I believe Scientific Assessment is not required.
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A.
Investigational Drug Services # (if applicable)	N/A.
Version Number/ Date:	Version 5 08/09/2023

ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submissio**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff*	**Approval must be received prior to IRB committe e/ designate d review.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff* *Contact: medreg@umn.edu* *See: https://policy.umn.edu/*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided.* *Contact: hrpp@umn.edu*	**Consider seeking approval prior to IRB submissio n.**
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process.* *Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee.*	**Approval from these committe es must be received prior to IRB approval;**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review* *Contact: ande2445@umn.edu*	

☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	**These groups each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core (BPIC) Formerly the AHC Information Exchange	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact:* bpic@umn.edu	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☐ **Yes** ☒ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff*	**Does not affect IRB approval.**

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2	8/17/22	Added details re: adverse effects in section 13.0 Modified consenting process will always be in person, section 21.0 Changed population of "fear of negative consequences…" as excluded, section 9.0 Deleted "serious health conditions…" section in section 9.0	yes
3	8/29/2022	Removed population susceptible to coercion"	No
4	12/20/2022	Changed tDCS intervention from cathodal to anodal (per recent evidence) and increased the behavioral intervention from 30 minutes to 45 minutes (per recent evidence). Anodal electrode will be placed over right cerebellum, cathode electrode will be placed over right deltoid (per recent evidence re: placement) Changed working memory task from Wisconsin Card Sorting task to N-back task (per recent evidence and recommendations from colleagues using these tasks) Students have just finished training and we finalized the SOP. Recruitment will begin in mid January.	No

5	08/09/2023	Remove history of migraine from exclusionary criteria. Change “history of seizures” to history of seizures within the past 12 months. Confirmation of non-fluent aphasia diagnosis is requested to be changed from only physician or clinician report or Assessment using the Western Aphasia Battery to add “informal language assessment conducted by the PI”. Because PI is a certified, licensed speech-language pathologist, characteristics of non-fluent aphasia become apparent during the interaction with the potential participant through questions and answers about the study and through the screening process. Changes made to protocol (pages 20-21) and screening form	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

Anodal Transcranial Direct Current Stimulation (a-tDCS)
Constraint-induced language therapy (CILT)
Dorsolateral Prefrontal Cortex (DLPFC)
Electroencephalogram (EEG)
Quality of Life (QOL)
Speech-Language Pathologist (SLP)
Transcranial Direct Current Stimulation (t-DCS)
Dento-thalamic-cortical tract (DTC)
Functional magnetic resonance imaging (fMRI)
Principal Investigator (PI)
Clinical Translational Research Services (CTRS)
Biostatistical Design and Analysis Center (BDAC)
Standard Operating Procedures (SOP)
Statistical Package for the Social Sciences (SPSS)
Stroke and Aphasia Quality of Life Scale (SAQOL)

1. Objectives

1.1. Purpose:

To determine the effect of combining constraint-induced language therapy (CILT) with cerebellar tDCS in individuals with non-fluent aphasia after stroke.

The primary aims are to 1) determine the effect of combining cerebellar tDCS with constraint-induced language therapy (CILT) on language as measured by a verbal fluency task and discourse analysis task in a prospective, crossover study of adults with non-fluent aphasia after a cortical stroke and 2) demonstrate feasibility and data collection to inform a larger study.

The secondary aims include impact of the combined intervention on 1) resting state spectral EEG as measured through delta wave percentage 2) working memory as measured by the score on the Wisconsin Card Sorting Test and 3) quality of life as measured by the Stroke Aphasia Quality of Life survey tool. A final secondary aim will be to identify the tolerance of the intervention and barriers to participation measured by the adverse events questionnaire.

2. Background

2.1. Significance of Research Question/Purpose:

Information gained from this study will drive changes to the methodology for a larger clinical trial that will minimize attrition and help determine robust outcome measures.

Non-fluent aphasia occurs after a focal injury to the expressive language regions of the cortex, most often after a stroke and is characterized by limited verbal language and intact comprehension of language. While efficacious behavioral interventions have been identified, they are few and rarely lead to complete language recovery. The loss of effective, efficient expressive language can have a devastating impact on social relationships, return to work, independence and mental health, to name a few. Identification of novel, effective interventions for non-fluent aphasia has been identified as a key research priority in the field of speech-language pathology.

Preliminary data will provide valuable information about the potential of combining CILT with right cerebellar anodal tDCS to positively impact language and working memory in non-fluent aphasia. The dento-thalamic-cortical tract (DTC) is the primary pathway between the cerebellum and cortex and has recently been implicated in non-fluent aphasia. A better

understanding of the role of the DTC and its potential for neuroplastic change after cortical stroke will be included in the interpretation. Neurophysiologic data from EEG will reveal not only the impact of tDCS on alpha and delta bands but the relationship to discourse. Finally, we will be able to document changes to quality of life and determine if changes are related to the experimental intervention.

From an educational perspective, this project will provide a valuable inter-professional experience for graduate students from the Departments of Communication Sciences and Disorders and Department of Computer Science. Such cross-college collaborations are an institutional priority on the University of Minnesota, Duluth campus.

This body of work has the potential to lead to the development of a new intervention protocol for non-fluent aphasia and provide the neurophysiologic rationale for the changes observed. Together, this will drive the field of neurorehablitiation forward in creating novel, innovative interventions for optimal functional recovery.

2.2. Preliminary Data: N/A

2.3. Existing Literature:

The study of neuroplasticity has provided much needed insight into mechanisms of neural recovery which has launched a shift in the way rehabilitation professionals plan intervention for individuals after stroke and brain injury. Now, greater attention is given to the type and amount of behavioral, task-specific practice that is thought to promote long-term potentiation and experience dependent plasticity. However, functional recovery after stroke and brain injury is still, often incomplete, negatively impacting independence and return to social, vocational and community engagement.

Intensity of rehabilitation has been identified as a key research priority by a number of authors(Cherney et al., 2008, 2011; Marangolo, 2020). Specifically, CILT reportedly has an 86% evidence to clinical use gap and therefore, requires additional study (Shrubsole et al., 2018).

Another research priority identified by Marangolo and colleagues (2020) was to better determine the potential effects of cerebellar tDCS on language in individuals with aphasia. Many reports have confirmed connectivity between the right cerebellar hemisphere and the left cortex, specifically the frontal and prefrontal cortical regions (Stoodley, 2012). These regions are

associated with expressive language, motor planning and programming and cognition. In fact, the right cerebellum has been shown to play a role in word retrieval and generation, working memory, language learning and semantic processing (Murdoch, 2010; Stoodley, 2012) and diaschesis in the right cerebellum has been shown in chronic non-fluent aphasia (Abe et al., 1997). This, paired with the distance from the stroke lesion site makes the right cerebellum a desirable location for stimulation. The combination of tDCS behavioral language intervention has resulted in improved naming in individuals with aphasia (Sebastian et al., 2017, 2020; Turkeltaub et al., 2016). However, there has been no evidence regarding other functional language skills such as discourse.

Finally, another research priority has been the inclusion of neurophysiologic measures in intervention studies to better understand the neural underpinnings of the experimental intervention (Cherney et al., 2008, 2011). Although functional magnetic resonance imaging is the tool most often recommended, it has many contraindication such as cost, availability, and individual comfort and tolerance. Although EEG acquires different data than fMRI, it is a measure of neurophysiology. It is also non-invasive, more accessible and cost-effective, fairly fast to acquire and well-tolerated. Resting state EEG has been identified as a viable tool to investigate electrical brain activity in those with post-stroke aphasia (Dalton et al., 2021) and is sensitive to changes after tDCS (Boonstra et al., 2016). Since an increase in delta frequency bands has been associated with the language deficits observed in aphasia (Hensel et al., 2004; Spironelli & Angrilli, 2009), one would hypothesize it may be a sensitive measure to determine the neurophysiologic impact of a language intervention such as that in the proposed study. In addition, an increased peak alpha frequency has been associated with improved attention and "cognitive preparedness" which would also be an expected outcome of the proposed intervention.

This pilot study has the potential to inform a larger, externally funded clinical trial that may lead to an innovative, novel approach to improve functional language in those with non-fluent aphasia.

3. Study Endpoints/Events/Outcomes

3.1. Primary Endpoint/Event/Outcome:

Primary outcome variables include:

1) Main Concept Discourse analysis using standardized picture description "Broken Window", story retell "Cinderella" and procedural narrative "how

to make a peanut butter sandwich". Each task has established standards and a scoring system for responses. Scoring is categorical and includes: accurate and complete=3, accurate and incomplete =2, inaccurate and complete=2, inaccurate and incomplete =1 and absent response =0 (Richardson & Dalton, 2016). *Hypothesis: We hypothesize the raw score of each of the discourse measures (picture, story and procedure) will significantly increase after the real tDCS intervention, but not after the sham intervention.*

2) Verbal Fluency is assessed by asking the participant to name as many animals as they can in one minute and then as many words that start with /f/ as they can in one minute. The tester collects a tally of how many animals and words that begin with /f/ were produced by the participant which is used as a raw score, scaled. If the participant names items that are not within those categories, those responses are not counted in the tally. These tasks are valid and reliable and used throughout aphasia literature. Hypothesis: We hypothesize the raw score of the verbal fluency measures will significantly increase after the real tDCS intervention, but not after the sham intervention.

These data will be collected at four points in time:

1) *Initial baseline;*
2) *post intervention (A or B);*
3) *Follow-up baseline (after washout period);*
4) *post intervention (A or B)*

3.2. Secondary Endpoint(s)/Event(s)/Outcome(s):

1. Working memory has been shown to play a role in non-fluent aphasia. Working memory is assessed using the N-back task. Scoring is binary and each response is either scored as correct=1 or incorrect =0 to obtain a raw score that is a scaled variable. We are interested in learning if the working memory score changes after intervention and if the change has a relationship with any changes in language as measured above in the primary endpoint. *Hypothesis: We hypothesize the working memory score will significantly increase after the real tDCS intervention, but not after the sham intervention. We also hypothesize a significant positive relationship between the working memory score and the scores across all three discourse tasks.*

These data will be collected at four points in time:
1) Initial baseline;
2) Post intervention (A or B);

3) Follow-up baseline (after washout period);
4) Post intervention (A or B)

2. An increase in delta wave percentage during resting state EEG has been shown in individuals with aphasia. The standard practice is to conduct a 2 minute resting state EEG while eyes are open. Data is then processed through EEGLab in MATLab to "pull out" the amount of delta wave bands/ total wave bands to identify a percentage of delta waves within the 2 minute sample. We are interested in learning if this delta percentage changes after intervention and if the change may be associated with any changes in language as measured above in the primary endpoint. The delta wave value is calculated by dividing the number of delta waves present/ total waves within the 2 minute sample and represented in a percentage. The delta wave percentage will be calculated for each of the following EEG locations: Fp1, F3, F7 and Fz of the 10/20 International EEG system. This would provide a neurophysiologic rationale for the changes in language. *Hypothesis: We hypothesize the delta percentage to significantly decrease after the real tDCS intervention, but not after the sham intervention. We also hypothesize a significant negative correlation between the delta percentage and scores across the discourse tasks, with lower delta wave percentage, language scores will be higher.*

These data will be collected at four points in time:
1) Initial baseline;
2) Post intervention (A or B);
3) Follow-up baseline (after washout period);
4) Post intervention (A or B)

3. Quality of Life will be assessed using an abbreviated version of the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39) (Hilari et al., 2003)), which uses a Likert Scale 1-5. Completion of the SS-QOL results in a raw score, which will be a scaled variable. We are interested in the relationship between QOL and changes in language as measured above. *Hypothesis: We hypothesize the raw score of the SAQOL will significantly increase after the real tDCS intervention, but not after the sham intervention. We also hypothesize the score on the SAQOL will be positively and significantly correlated with scores across the discourse tasks.*

These data will be collected at four points in time:
1) Initial baseline;
2) Post intervention (A or B);
3) Follow-up baseline (after washout period);
4) Post intervention (A or B)

4. An adverse events/experiential survey will be given to participants to provide using a Likert Scale 1-4. In addition two open ended questions will be asked about positive experiences and negative experiences to help us identify barriers to participation. The objective portion will provide us a raw score and the open ended questions will be analyzed qualitatively for agreement and themes. This information will be used to hone the methodology to improve retention and reduce attrition in a larger clinical trial. This survey will be provided at the end of the experience. If a participant drops out, the research team will reach out to ask the participant to complete the survey to assist us in establishing better methodology.

4. Study Intervention(s)/Investigational Agent(s)

4.1. Description:

There will be two intervention conditions in this study:

1) anodal tDCS (2mA) to the right cerebellum; and

2) sham tDCS to the right cerebellum.

The participants will receive 20 minutes of tDCS (sham or real) during constraint-induced language therapy (CILT) followed by an additional 20 minutes of CILT alone.

tDCS (TCT Research Limited; Hong Kong): 5x5 saline-soaked sponge electrodes will be used with the anode placed over the right cerebellar hemisphere; 1cm under and 4cm lateral of the inion targeting lobule VII and the anode will be placed on the right shoulder (Ferrucci et al., 2015; Sebastian et al., 2020). The electrode placement will be the same across both conditions.

CILT: The CILT behavioral intervention will be led by a certified, licensed speech-language pathologist and a graduate student assistant and will follow the guidelines of CILT (Maher et al., 2006; Mozeiko et al., 2016; Pulvermuller et al., 2001). During the behavioral language intervention, participants will engage in language activities such as card games that require verbal expression. Other forms of communication such as gestures and writing will be discouraged and only verbal output will be encouraged through the use of cues and, when needed, models.

As this is a within subject study, all participants will experience both intervention conditions through a cross over design. Each condition will

involve 12 intervention sessions across 4 weeks; 3 sessions/week with a 4-week washout period between conditions.

We believe this study meets the criteria for NSR-IDE because (1) Is not an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject; (2) Is not purported and will not be represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) Will not be used of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject; and/or (4) Does not otherwise pose a potential for serious risk to the health, safety, or welfare of a subject.

The sponsor-investigator agrees to comply with the abbreviated IDE requirements in 21 CFR 812.2(b)

4.2. Drug/Device Handling: N/A

4.3. Biosafety: N/A

4.4. Stem Cells: N/A

4.5. Fetal Tissue: N/A

5. Procedures Involved

5.1. Study Design:

Within subject, crossover prospective pilot study.

5.2. Study Procedures:

Potential participants will be recruited through the Robert F. Pierce (RFP) Speech-Language and Hearing Clinic on the UMD campus and surrounding communities including stroke support groups and public advertisements using paper and digital flyers. Digital flyers will also be used as posts to the Neural Function and Recovery Lab research lab social media page(s) and the lab website. Past and current clients of the RFP Speech-Language and Hearing Clinic, with a diagnosis of non-fluent aphasia, will be sent a paper flyer in the mail and will be informed of the study by their current graduate student clinician. In addition, paper flyers will be posted in the lobby of the Robert F. Pierce Speech-Language and Hearing Clinic.

Participants will be screened for eligibility using the screening form (in supplementary documents) to ensure they meet the eligibility requirements. Screening can be done in person or via phone. The individual must provide documentation of a left hemisphere stroke in the form of a physician or clinician report and diagnosis of non-fluent aphasia in the form of a physician or clinical report. If they do not have documentation of their stroke, we will obtain consent from the interested participant to request the medical report. If they do not have documentation of their aphasia diagnosis and are still interested in participating, we will either obtain a consent from the interested participant to request the SLP assessment report or the research team will administer the Western Aphasia Battery Assessment to determine the type and severity of aphasia. Once deemed eligible, a member of the research team will go over the consent form with the individual in person and answer any questions the individual has. Both the participant and research team member will sign the consent form to certify it and a copy will be provided to the participant. Paper copies will then be scanned and stored in Advarra EDC. If the participant is screened through a phone meeting or via virtual visit on Zoom, the consent form will be discussed and shared with the participant through email. Upon coming in for the first baseline assessment visit, the consent form will then be signed.

Part of the consent requires participants to not engage in other speech-language therapy sessions outside of those provided in the study. For example, an individual who is currently receiving speech-language therapy services at the RFP Clinic who consents and is enrolled in this study would then only receive the intervention visits outlined in this study for the duration of their enrollment of the study and would then resume speech-language therapy services at RFP Clinic once their participation ends. Careful consideration will be given to those who receive insurance benefits that cover speech-language therapy services at other clinics to ensure a participant won't "lose" insurance coverage for stepping away from traditional speech-language therapy sessions for a 2-month time span. This is typically only an issue for individuals receiving benefits from Medicare A. The PI will talk with potential participants regarding this issue.

Participants will attend 17 visits over the course of 2 months, including one visit for screening and consenting process. The screening and consenting visit is expected to last ~30 minutes. If formal testing is needed for the aphasia diagnosis to be confirmed, the screening and consenting visit will last ~90 minutes. Each assessment/data collection visit is expected to last 60-75 minutes. Intervention visits are expected to last 60 minutes for total

of 21.5 hours of participation over the course of the study. If a participant misses an intervention session, we will attempt to make it up during that same week of intervention and reschedule the assessment day. The timing of the assessment day post intervention is critical as tDCS does not appear to have long-lasting effects. The post intervention assessment visit would have to take place within 1-2 days of the last intervention day. If rescheduling is not an option, the total number of intervention sessions attended will be noted in the data. However, if 2 sessions have been missed within either of the intervention periods, the participant will need to be re-enrolled or dropped from the study. Participants will be randomly assigned to receive either the real or sham tDCS first.

Schedule of Events

Table 1. Schedule of Research Activities.

	Screen /	Baselin	Interventio n A or B	Follow-Up 1	Washout	Baselin e 2	Interventio n A or B	Follow-Up 2
Day/Week	Visit 1	Visit 2 Anytim e after consent	Visits 3-8 6 total sessions: 3 sessions per week across 2 weeks). Must occur	Visit 9 must occur within 1 day of visit 8	4 weeks	Visit 10 can occur anytim e after the 4 week washo ut	Visits 11-16 6 total sessions: 3 sessions per week across 2 weeks Must occur within 5	Visit 17 must occur within 1 day of visit 16
Screen for Eligibility	x							
Consenting Process	x							
Western Aphasia Battery	If needed							

Urine Pregnancy Test	Only if within child-bearing years							
Discourse Analysis		X		X		X		X
Verbal Fluency		X		X		X		X
N-back (working memory)		X		X		X		X
Resting state EEG		X		X		X		X
Stroke-Aphasia Quality of Life Survey		X		X		X		X
Adverse Events			X	X			X	X
Sham OR Real tDCS+CILT			X				X	

<u>Data Collection / Assessment Sessions:</u>

Participants will be seated comfortably in a chair or in their wheelchair with an adjustable table in front of them. A member of the research team will sit directly across from the participant and present assessment stimuli for the discourse analysis. Discourse analysis will take approximately 15 minutes and will include picture description, story retell and a procedural narration. The verbal fluency test involves naming as many animals as they can in one minute followed by naming as many words starting with /f/ as they can name in one minute. The total time for the verbal fluency task is <5 minutes. N-back will be given using the laboratory computer and takes approximately 10 minutes to complete. These tasks will be videotaped for the purposes of accurate data collection of participant verbal responses. This is necessary for accurate data collection as mild forms of aphasia are harder to assess in real time and may require careful examination of a video. All recordings will be made using Zoom and stored in UMN Box. All temporary files

will be immediately deleted once uploaded to Box. After the behavioral assessments have been completed, the participant's head will be measured and fit with the EEG cap and electrodes (~15 minutes) and three 2-minute resting state EEG (eyes open) will be done. Finally, the participant will be given the SAQOL questionnaire with as much assistance is needed for reading and/or interpreting the meaning of questions. A visual Likert scale will be provided as a support for language if need be. The participant will be offered breaks between tasks as needed. The research team ran a trial data collection session with one of the members of the research team who provides responses similar to that we would expect of an individual with non-fluent aphasia. The data collection session lasted 75 minutes. One graduate student will be running the EEG portion of the experiment and has been trained and has shown competence in placement of electrode cap and use of the EEG data software. One graduate student will be running the language portion of the experiment and has been trained and has shown competence in the administration and scoring of the discourse, fluency and working memory tasks.

Intervention Sessions:

Participants will be seated comfortably in a chair with armrests during both the intervention and assessment visits. The assessment and intervention tasks can also be conducted while seated in a wheelchair if need be. Skin where the tDCS electrodes will be placed will be gently cleaned using an alcohol swab and hair will be separated and clipped to allow the electrode to be placed. Two saline-soaked t-DCS sponge electrodes (25 cm^2) will be used. The anode placed over the right cerebellar hemisphere, 1-2cm below the inion and 3-4cm lateral to the inion (Ferrucci et al., 2015; Grimaldi et al., 2016) *and the cathode electrode will be placed on the right deltoid region. Electrodes will be kept in place with the neoprene/Velcro head band in the tDCS device kit. The device will be programmed for "real" or "sham" setting for a 20-minute duration using the setting buttons on the device. If the device is programmed for "real" tDCS, the intensity will gradually increase over the first 30-45 seconds to the designated value of 2mA and remain at that setting until it gradually decreases in intensity over the last 30-45 seconds of the 20-minute duration. If "sham" is selected, the gradual ramp up occurs followed by the ramp down. Therefore, no stimulation is provided during sham condition. While the PI is placing the electrodes, the graduate intern will be setting up the behavioral language activity (CILT) for the session. Once the electrodes are in place, the device is programmed and the behavioral activity is set up, the intervention will begin. The tDCS device will be turned on (to either real or sham) and the participant will engage in the*

behavioral intervention. The total intervention session will last for 45 minutes: 20 minutes of combined c-tDCS and CILT and the final 25 minutes CILT only. After each intervention phase, the participant will be asked to complete a short adverse effects survey which will help the research team make modifications for a larger clinical trial. The research team ran a trial intervention session with one of the members of the research team who provides responses similar to that we would expect of an individual with non-fluent aphasia. The intervention session lasted 60 minutes including placing and removing of electrodes. All members of the research team will be trained in the methods of placing electrodes and demonstrate competence. However, for this study, the PI will do all of the electrode placement. The placement of the electrodes for cerebellar stimulation is well described in the literature. For a larger clinical trial, inter-rater reliability for electrode placement will be done in order to ensure consistency among research staff.

5.3. Study Duration:

Each intervention session will be scheduled for 60 minutes to allow for set up, take down and questions from the participant. Each condition (Sham and Real tDCS) will consist of 6 intervention visits (3x/week across 2 weeks) with a 4-week washout period between conditions. After the washout period, the participant will then engage in 6 intervention visits of the opposite intervention. The intervention visits do not have to be consecutive within the intervention week.

The total duration of participant participation will be 17 visits across 2 months. The duration anticipated to enroll all study participants is expected to be 18 months. It is anticipated that it will take 36 months to complete all study procedures including data analysis.

5.4. Individually Identifiable Health Information:
Name, date of birth, medical diagnosis (cortical stroke) and communication diagnosis (type of aphasia) will be collected from the participant and records provided by the participant (specifically, the speech-language pathologist report).

5.5. Use of radiation*: N/A*

5.6. Use of Center for Magnetic Resonance Research*:* N/A

6. Data and Specimen Banking

6.1. Storage and Access: N/A

6.2. Data: N/A

6.3. Release/Sharing: N/A

7. Sharing of Results with Participants

7.1. Sharing Results: A brief summary of study results will be shared with each participant upon completion of the study along with a "Thank you" note for their participation (See thank you letter in supplemental documents).

7.2. Sharing Genetic Results: N/A

7.2.1 Disclosure of Results: N/A

7.2.2 Returning Results to Participants: N/A

Aggregate or individual results: N/A

Laboratory results: N/A

Plan for return of results to participants: N/A

Types of results to be returned to participants: N/A

7.2.3 Future analysis of genotypes: N/A

8. Study Population

8.1. Inclusion Criteria:

Eligible participants must be over the age of 18 years, have a history of stroke and diagnosed with non-fluent aphasia. The individual can provide documentation of aphasia in the form of a physician or clinician report. If they do not have documentation of their their aphasia diagnosis, we will either obtain a consent from the interested participant to request the speech-language pathology assessment report, the PI can conduct an informal language assessment to confirm the diagnosis. Or, if it still unclear,

the PI will administer the Western Aphasia Battery Assessment to determine the type and severity of aphasia.

In addition, eligible participants must be able to independently understand simple directions, use some speech to communicate, have access to reliable transportation (including taxi and/or other transportation services), fluent in English.

8.2. Exclusion Criteria:

Pregnancy, history of seizures within the past 12 months, any metal implants in the body such as pacemaker, cochlear implant, aneurysm coil or clip (excluding dental fillings), , psoriasis or eczema affecting the scalp, history of a head injury such as a concussion or diagnosis of a mental health or neurological condition/disease.

8.3. Screening:

The screening process will involve the research staff asking screening questions of the potential participant (screening form is in supplemental documents). This can be done either by phone, virtual visit or in-person (screening phone script is in supplemental documents). If the individual does not have documentation of an aphasia diagnosis, the PI, who is a licensed, certified and experienced speech-language pathologist will conduct an informal assessment through conversation and simple language tasks to ensure the diagnosis of non-fluent aphasia. If the diagnosis is still unclear, the PI will conduct the Western Aphasia Battery either through an in-person visit or via virtual visit to confirm the diagnosis of non-fluent aphasia. If the research staff member is a graduate student, they will be supervised by the PI, who is a licensed and certified speech-language pathologist. Graduate students in speech-language pathology programs are qualified to administer and interpret this test under the supervision/ guidance of a licensed, certified speech-language pathologist. If the participant is within child-bearing years, a urine pregnancy test will be provided during the first in-person visit prior to consenting.

9. Vulnerable Populations

9.1. Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be the focus of the research (targeted), included but not the focus of the research excluded from participation in the study.
Children	Excluded
Pregnant women/fetuses/neonates	Excluded
Prisoners	
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	
Non-English speakers	
Those unable to read (illiterate)	
Employees of the researcher	
Students of the researcher	
Undervalued or disenfranchised social group	
Active members of the military (service members), DoD personnel (including civilian employees)	
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	

Individual or group with a serious health condition for which there are no satisfactory standard treatments.	
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	

9.2. Additional safeguards, if any, to ensure inclusion is appropriate:

Active members of the military (service members), DoD personnel (including civilian employees): Members of the military may not be known, research staff will not be asking a direct question about military status to potential participants. We do not anticipate vulnerability for this group to be increased by participating in this study.

Undervalued or disadvantaged social group: Undervalued or disadvantaged people may not be known, research staff will not be asking a direct question about socioeconomic status to potential participants. We do not anticipate vulnerability for this group to be increased by participating in this study.

Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare: Undervalued or disadvantaged people may not be known, research staff will not be asking a direct question about socioeconomic status to potential participants. However, we have taken special precaution to make sure participants are fairly and adequately compensated for their time in this study, yet not coerced by unreasonably high compensation amounts.

9.3. If research holds prospect for direct benefit to participants, provide justification for any exclusions indicated in the table above:

Effects of any non-invasive brain stimulation technique on an unborn infant is unknown, therefore women who are pregnant are excluded from any study involving these techniques. In order to complete the language and working memory tasks required, individuals must be fluent in English and be able to read. There are currently no normative data for these tasks in other languages. Individuals with serious health conditions will be excluded from the pilot due to the number of visits required for the study as individuals from this groups may not be able to consistently attend and/or complete the required number of visits. However, a larger clinical trial could offer the intervention sessions in the individual's home, requiring the participants to only come in for the data collection/assessment sessions. At that time, this population will not be excluded.

10. Local Number of Participants

10.1. Local Number of Participants to be Consented: *A total of 5 participants will be enrolled with the goal of 3 participants to complete the duration of this pilot study.*

11. Local Recruitment Methods

11.1. Recruitment Process:

Paper flyers will be available in the Robert F. Pierce (RFP) Speech-Language and Hearing Clinic on the UMD campus. In addition, a poster of the flyer will be posted in the lobby of the clinic. The flyers (and poster) will have contact information for the research team, both email and phone. Interested individuals can contact the research staff for more information. The research staff will also request permission from the client to come into one of their speech-language therapy sessions at RFP to talk with them about the study to gauge their interest.

Flyers (paper and digital) will also be shared with local support groups, speech-language pathologists working in medical settings who are alumni of the UMD master's program, local medical community and other sources including speech-language pathology community platforms. The research team will reach out to local stroke support groups to inform them of the study and request to attend a meeting to share information about the study with members of the support group.

To minimize attrition, a "Welcome Packet" will be provided to each participant including an individual schedule of each visit, contact information for the research staff, transportation scheduling information (if needed). Research staff will offer to assist in making transportation arrangements if needed. Weekend and evening visits can be scheduled to accommodate the participants' schedules as some may need to have a caregiver attend the sessions with them due to physical limitations, inability to drive, etc. The participant will be asked their preference re: communicating with the research team. The team will then provide regular updates and reminders through that preferred communication method (phone, text, email). During the intervention phases, the research team will be in daily contact with the participant to check in, confirm transportation and answer questions.

If the participant is already an RFP client, the study visits will take the place of their regularly scheduled clinic visits at RFP. Breaks will be offered both during assessment/data collection days and intervention days as needed with the exception of the tDCS application. Once the stimulation begins, ideally it should be provided without a break for that 20 minutes. If an individual expresses discomfort, additional saline solution is applied to the electrodes. If the individual continues to express discomfort, the tDCS will stop. The research team does not anticipate this as very few adverse effects have been reported using tDCS. Bottled water and light cookies/crackers will be available to the participant.

11.2. Identification of Potential Participants:

Interested individuals will contact research staff either through email or phone. Or, in person, if they are clients in the RFP Clinic.

11.3. Recruitment Materials:

Potential participants will be recruited through the Robert F. Pierce Speech-Language and Hearing Clinic on the UMD campus and surrounding communities including stroke support groups and public advertisements using paper and digital flyers. Digital flyers will also be used as posts to the Neural Function and Recovery Lab research lab social media page(s) and the lab website. Past and current clients of the RFP Speech-Language and Hearing Clinic, with a diagnosis of non-fluent aphasia, will be sent a paper flyer in the mail and will be informed of the study by their current graduate student clinician. In addition, paper flyers will be posted in the lobby of the Robert F. Pierce Speech-Language and Hearing Clinic.

11.4. Payment:

Participants will receive $150 at the end of the first intervention phase, another $150 at the end of the second intervention phase and a $150 bonus for completion of the study. Participants will be required to sign a log each time payment is received. Payment will be in the form of adding money to a ClingCard given to the participant.

12. Withdrawal of Participants

12.1. Withdrawal Circumstances:

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- *Pregnancy*
- *Significant study non-compliance*
- *If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant*
- *If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation*

12.2. Withdrawal Procedures:

If a participant wishes to withdraw or we determine that the participant should withdraw, we will terminate data collection and discuss with the participant the reasons for withdrawal. All data collected up to that point will be used in analysis unless the participant wishes for their data not to be used.

12.3. Termination Procedures:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination.

13. Risks to Participants

13.1. Foreseeable Risks: There is *a possibility that some participants may face fatigue, embarrassment, frustration, or other challenges by participating in the study. Participants will be encouraged to take breaks to mitigate these experiences. Participants will also be reminded that participation in the study is voluntary and as such, they are not required to complete any components of the study and may skip questions or assessments entirely. Reports of tingling/itching sensation under the electrode is the most commonly reported adverse effect (Nitsche 2008, Table 1). Although there have been reports of skin burn at the electrode site after tDCS, these cases were not following safety guidelines and occurred due to extended stimulation periods of 30 minutes, drying of electrode, abrading skin surface prior to stimulation and using tap water to soak the electrodes When tDCS is used in line with safety guidelines, such as this study proposes, using saline soaked electrodes, keeping electrodes soaked well, 20 minute stimulation time, no burns or heating of the electrodes or scalp were avoided. For review, see* (Antal et al., 2017; Matsumoto & Ugawa, 2017) *Although the tDCS current is well below threshold of tissue damage, individuals post stroke are more likely to have seizures. Therefore, the majority of tDCS safety protocols exclude anyone who has had a history of seizures as an additional safeguard. For review, see* (Antal et al., 2017; Matsumoto & Ugawa, 2017)*. In addition, although no negative effects have been observed from tDCS in women who are pregnant or the fetus, there is too little evidence and most protocols exclude this population until more is known or until the benefits to the patient outweigh the potential risk* (Antal et al., 2017)*. The electroencephalogram (EEG) is collecting data from the brain, not stimulating it, therefore, far fewer, if any risks are associated with EEG. Previously, EEG electrodes had to be placed by abrading the skin and using an adhesive to attach them which often led to risk of infection* (Ferree et al., 2001)*. However, there are now saline soaked electrodes which do not need to be adhered to the skin such as those used in this protocol that have similar impedance values of the more "traditional electrodes"* (Ferree et al., 2001)*.*

Privacy/Confidentiality Risks*: Risk of loss of confidentiality is unlikely, but could possibly occur as PHI is utilized as part of this study. This risk would be minimized by protections such as de-identification of participants via use of a study identifier, locked/secured/limited access to PHI, and electronic data securely stored and password-protected.* See also adverse events in 18.2

13.2. Reproduction Risks: *Although there have been no adverse side effects of tDCS to women who are pregnant, all neuromodulation studies exclude this population due to unknown impact to an unborn baby.*

13.3. Risks to Others: N/A

14. Potential Benefits to Participants

14.1. Potential Benefits:

There is a potential for a transient improvement in language expression and working memory after participating in the study.

15. Statistical Considerations

15.1. Data Analysis Plan:

All data will be de-identified and entered into Excel and SPSS for analysis. Visual analysis will be conducted initially with plotting of descriptive statistics.

15.2. Power Analysis:

A literature review of studies measuring the impact of cerebellar tDCS in aphasia did not find usable estimates of variation (SD, SEM, IQR, etc.) for the outcomes of interest. Accordingly, using a standard effect size scale (Cohen's d, scaling the treatment effect size relative to between-participant SD), and a range of plausible within-participant correlations of +0.4 to +0.9, we estimate that enrolling 4 participants will provide 80% power to detect large (d=0.9) to very large (d=2.3) treatment effect sizes using a two-sided 5% significance level.
A post-hoc power analysis will be conducted using the information gathered in the pilot study to determine the sample size needed for a larger study.

15.3. Statistical Analysis:

BDAC was consulted regarding the plan for statistical analysis. Based on their recommendations, the following plan was created. Throughout the project, BDAC will be consulted to review this statistical analysis plan and provide additional insight to alternative statistical processes best suited for the data as needed.

- *The quantitative data for attrition rate and adverse events will be descriptive in nature and will be reported as counts and rates. The*

open-ended questions regarding barriers to participation will be analyzed to identify common themes.

- *Primary outcome measures, main concept discourse scores and verbal fluency counts, will be compared between treatment conditions using mixed effects generalized linear models, with fixed effects for treatment, period, sequence, pre-post time point, and treatment by pre-post time point interaction, and random effects for participant within sequence. This will provide difference-in-differences (post-treatment minus pre-treatment) estimates for the treatment effect which will be reported along with 95% confidence intervals as a measure of precision. Similar models will be used to analyze the secondary outcome measures including WI card sorting task, EEG delta wave, and SAQOLL.*

- *Estimates from these models will provide important information for planning a well-powered clinical trial that are not obtainable elsewhere. Estimates that will be gathered in this pilot trial that will inform the subsequent power calculation include the treatment effect size, within-participant correlation of repeated measures, and random effects variance, for each of the outcome measures.*

- *Pearson's Correlation will be conducted to determine the relationship between primary outcome variables (discourse and working memory scores) and SS-QOL as well as other scaled demographic variables such as age and duration since stroke.*

- *Spearman's Rho Correlation analyses will be conducted to determine the relationships between primary outcome variables (discourse and working memory) and EEG data, reported in percentage.*

- *The multivariate repeated measures and correlation analyses may not be terribly informative as the pilot sample size may lack the power for these statistics. However, they may be useful in descriptive interpretation of the data and lay the foundation for the larger clinical trial.*

15.4. Data Integrity:

Data collection is the responsibility of the research team under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All research staff will have extensive training in the procedures of data collection by following the Standard Operating Procedures for the study. Behavioral data (scores on discourse tasks, Wisconsin Card Sorting, verbal fluency) will be collected on a paper data form (see supplemental

documents), using participant code. The EEG data will be stored within MatLab, again using participant code. Data will then be entered into a de-identified excel document stored UMN Secure Box and transferred into an SPSS file when preparing for statistical analysis. The SPSS files will also be deidentified. The de-identified excel and SPSS files will be stored in UMN secure Box folder. All IRB approved research staff will have access to these files in Box. The master database of participant names and codes will be kept in a digital file in UMN secure Box folder as well. IRB approved research staff will have access to this file as well. If research staff changes, ie: graduate student completes program and is transitioned off of the research team, they will be removed from the shared folder.

16. Health Information and Privacy Compliance

16.1. Select which of the following is applicable to your research:

☐ My research does not require access to individual health information.

X I am requesting that all research participants sign a HIPCO approved HIPAA

Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

16.2. Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

X I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

16.3. Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

All participants in this study will consent and sign a HIPAA authorization. Data will be collected directly from said participants with no review of their medical records.

16.4. Approximate number of records required for review: 5

16.5. Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

X Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We will communicate with participants via: proofpoint secure emails, telephone (using study-specific phone number), text message (if participant agrees by signing the consent for text message correspondence), unsecure email (if the participant agrees by signing the consent for unsecure email correspondence).

16.6. Explain how the research team has legitimate access to patients/potential participants:

16.7. Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

X In the University's Box Secure Storage (box.umn.edu)

X Store ☐ Analyze X Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☐ Other:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as a tablet or smartphone not previously listed

16.8. Consultants. Vendors. Third Parties: N/A

16.9. Links to identifiable data:
All data will be identified with an identification code unique to the participant. Study staff will keep the mapping of identification code to the

identity of the participant on an encrypted password protected computer stored separately from the data in Box. That same identification code will be used for data-entry into Box. Any internal data reports will use only these codes and will not use any identifiable information. Any external data reports, abstracts, publications, presentations, etc. will present de-identified, grouped, and/or aggregate data. Any reports to the University of Minnesota IRB (such as Adverse Event reporting and annual renewal reports) will be kept confidential; they will not include participant-identifiable information; only the participant's identification code will be used.

16.10. Sharing of Data with Research Team Members:

Only IRB-approved members of the study team will have access to the data. Data will be shared through UMN Secure Box.

16.11. Storage of Documents:

Paper documents will be stored in a locked cabinet in a locked research office only accessible to research staff.

16.12. Disposal of Documents:

Disposal of all study documents will be in accordance with the university policy.

17. Confidentiality

17.1. Data Security:

All data will be securely stored in UMN Secure Box. De-identified data in the form of an excel data spreadsheet and SPSS data file will be securely stored in Box. The informed consent will NOT be placed in the participant's medical file or clinic file (if a client in the RFP Speech-Language Hearing Clinic).

18. Provisions to Monitor the Data to Ensure the Safety of Participants

18.1. Data Integrity Monitoring.

The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

Independent monitoring of the clinical study for clinical protocol compliance will be conducted by University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service.

The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and State regulations).

Frequency of monitoring visits will occur:

- *After IRB approval*
- *As soon as possible after the first subject is enrolled*
- *During the study data collection phase*
- *After the last subject has completed his/her participation in the study*

This monitoring schedule may be revised based on the following considerations:

- *Accrual rate*
- *Protocol deviations or non-compliance with regulatory authorities*
- *Magnitude of data corrections required*
- *Study stage (e.g. start-up or follow-up)*
- *Complexity of the trial*
- *Request (IRB, Investigator, other etc.)*
- *DSMB recommendation*

Monitoring visits will be performed annually, at a minimum. The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

Primary responsibilities of the monitors will include verifying the following:

- *Investigator qualifications*
- *Facilities and equipment*
- *Storage, dispensing and disposition of investigational products*
- *Protocol compliance*
- *Informed consent*
- *Training and delegation of authority*
- *Subject eligibility*
- *Recruitment, screening and enrollment*

- *Verification of data and data clarification*
- *Adverse event reporting*
- *FDA correspondence*
- *Deviations*

18.2. Data Safety Monitoring

Adverse Event (AE) vs. Serious Adverse Event (SAE): An adverse event is any undesirable experience associated with the use of a medical product in a participant. A serious adverse event (SAE) should immediately be reported to the FDA when the participant outcome is:

- **Death:** Report if you suspect that the death was an outcome of the adverse event, and include the date if known.
- **Life-threatening:** Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
- **Hospitalization (initial or prolonged):** Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- **Disability or Permanent Damage:** Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- **Congenital Anomaly/Birth Defect:** Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- **Required Intervention to Prevent Permanent Impairment or Damage (Devices):** Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- **Other Serious (Important Medical Events):** Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with

breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Severity of an adverse event: The following guidelines will be used to describe severity of an adverse event.

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to study intervention: The following guidelines will be used to describe the "relatedness" of an adverse event.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate as "potentially related" soon after discovery, it can be flagged as requiring

more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

- **Unlikely to be related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- **Not Related:** The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness: The Investigator will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Reporting of adverse events: Information on all adverse events will be collected including the:

- Event description
- Time of onset
- Assessment of severity
- Relationship to study intervention
- expectedness
- Time of resolution/stabilization of the event

All adverse events occurring while on study will be documented appropriately regardless of relationship. All adverse events will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an adverse event. However, if the participant’s condition deteriorates at any time during the study, it will be recorded as an adverse event.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious adverse events) or 30 days (for serious adverse events) after the last day of study participation. At each study visit,

the investigator will inquire about the occurrence of the adverse event since the last visit.

The following are considered "Promptly Reportable Events" by the UMN IRB and will be reported as "Reportable New Information" within 5 business days of learning of the event:

- Unexpected Death: Unexpected death of a locally enrolled participant/subject who has not withdrawn from the research whether the death is considered related to the research or not. Death is considered unexpected if the risk of death is not listed in the consent form or is not listed as a possible event in protocol-related documents such as the IRB approved protocol or the Investigator's Brochure.
- Risk: Information that indicates a new or increased risk, or a safety issue.
- New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor summary report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk. Do not submit Investigational New Drug (IND) safety letters, Medwatch reports, or other such individual reports to the IRB unless, in the opinion of the investigator, the event or information in the report constitutes a UPIRTSO or the report requires a change to the protocol and/or the consent form.
- An adverse event that indicates a potential increase in risk or reduction in benefit (such as those that may prompt a change to the protocol or consent form).
- An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or to describe a new risk.
- Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
- Protocol violation that harmed subjects or others or that indicates participants/subjects or others might be at increased risk of harm.
- Complaint of a participant/subject that indicates participants/subjects or others might be at increased risk of harm or at risk of a new harm.
- Any changes significantly affecting the conduct of the research outside of the investigator's control or not directed by the investigator, e.g., a new therapy for the condition under study is proving highly effective.
- Harm: Any harm experienced by a participant/subject or other individual that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures.

- A harm is “unexpected” when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
- A harm is “probably related” to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.
- Non-compliance: Allegation of investigator or study team noncompliance or finding of investigator or study team noncompliance.
- Audit: Audit, inspection, or inquiry by a federal agency (e.g. FDA Form 483).
- Report: Data safety monitoring reports from councils, committees, or boards charged with data and safety oversight activities; or other reports such as FDA non-approval letters.
- Researcher error: Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Confidentiality: Unauthorized disclosure of confidential information.
- Protocol Deviation: Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- Incarceration: Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- Complaint: Unresolved subject complaint.
- Suspension: Suspension or premature termination by the sponsor, investigator, institution or other IRB.
- Unanticipated adverse device effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- Disqualification / Termination: Change in qualification of any member of the study team based on state medical board, hospital medical staff action, or other disqualification by professional board or employ.
- Information that is not listed above does not require reporting to the University of Minnesota IRB.

19. Provisions to Protect the Privacy Interests of Participants

19.1. Protecting Privacy:

Confidentiality of the research participants will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers.

All material will be used exclusively for research. Data obtained will be stored in a confidential database without direct identifiers. The principal investigator and designated study staff will have access to the linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which time any identifiers will be removed and data will be stored at a secure storage facility for 6 years. Access to the locked file cabinet will be given to the study coordinators and principal investigator only. Any study files that will be shared with the University of Minnesota will remove patient identifying information.

19.2. Access to Participants*:*

Participants will be fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to initiating any study procedures

20. Compensation for Research-Related Injury

20.1. Compensation for Research-Related Injury: *In the event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.*

20.2. Contract Language: N/A

21. Consent Process

21.1. Consent Process (when consent will be obtained):

During the in-person screening visit: Once deemed eligible through an in-person screening and the participant wishes to be enrolled in the study, a member of the research team will provide a paper copy of the consent form and read it to the individual and answer any questions the individual has. Both the participant and research team member will sign the consent form to certify it and a paper copy will be provided to the participant. At this time, the HIPAA Authorization form will also be signed by the participant. Signed paper copies of both the informed consent and HIPPA authorization will then be given to the participant and will be scanned and stored in Advarra EDC or UMN Secure Box, whichever is recommended by the IRB.

If the participant is screened through a phone meeting or via virtual visit on Zoom and deemed eligible, the consenting process will occur at the initial research visit using the procedures described above.Upon coming in for the first baseline assessment visit, the consent form will then be signed along with the HIPAA form. Signed paper copies will be provided to the participant and scanned and stored in Advarra EDC or UMN Secure Box, whichever is recommended by the IRB.

During the consenting process, the member of the research team will ask questions of the participant to ensure understanding of the study and consent form and will encourage the participant to ask questions.

21.2. Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3. Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

We are requesting a waiver of written/signed documentation of consent for the screening portion of this study. A short phone script will be read to the participant before any screening questions are asked. The participant will need to provide verbal consent to answering these screening questions before proceeding.

21.4. Non-English Speaking Participants: N/A

21.5. Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

21.6. Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.7. Adults Unable to Consent: N/A

- Permission:
- Assent:

- Dissent:

22. Setting

22.1. Research Sites:

All data collection will take place on the University of Minnesota Duluth campus in the Neural Function and Recovery Lab (107 Chester Park Building).

22.2. International Research: N/A

23. Multi-Site Research N/A

23.1. Study-Wide Number of Participants:

23.2. Study-Wide Recruitment Methods:

23.3. Study-Wide Recruitment Materials:

23.4. Communication Among Sites:

23.5. Communication to Sites:

24. Coordinating Center Research N/A

24.1. Role:

24.2. Responsibilities:

24.3. Oversight:

24.4. Collection and Management of Data:

25. Resources Available

25.1. Resources Available:

PI will complete 90 minute PI Primer training. The PI has graduate student support and will be writing a grant for a part-time research coordinator for this project. The PI also has acquired a 3 credit release for 2022-2023 AY to dedicate

to this project. The PI is expected to dedicate 5 hours per week to this project, with some weeks requiring more/less depending upon enrollment. The PI anticipates 10-12 hours per week for a part time research coordinator. Services from Clinical Translational Research Services (CTRS) have been and will continue to be used in the planning, execution and monitoring of the study as needed. In addition, BDAC will also continue to be used as a resource for assistance in the statistical analysis of the data.

26. References

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M. S., Hamilton, R., Haueisen, J., Herrmann, C. S., Hummel, F. C., Lefaucheur, J. P., Liebetanz, D., Loo, C. K., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*, *128*(9), 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001

Ferree, T. C., Luu, P., Russell, G. S., & Tucker, D. M. (2001). Scalp electrode impedance, infection risk, and EEG data quality. *Clinical Neurophysiology*, *112*(3), 536–544. https://doi.org/10.1016/S1388-2457(00)00533-2

Ferrucci, R., Cortese, F., & Priori, A. (2015). Cerebellar tDCS: How to Do It. *The Cerebellum*, *14*(1), 27–30. https://doi.org/10.1007/s12311-014-0599-7

Grimaldi, G., Argyropoulos, G. P., Bastian, A., Cortes, M., Davis, N. J., Edwards, D. J., Ferrucci, R., Fregni, F., Galea, J. M., Hamada, M., Manto, M., Miall, R. C., Morales-Quezada, L., Pope, P. A., Priori, A., Rothwell, J., Tomlinson, S. P., & Celnik, P. (2016). Cerebellar Transcranial Direct Current Stimulation (ctDCS): A Novel Approach to Understanding Cerebellar Function in Health and Disease. *The Neuroscientist*, *22*(1), 83–97. https://doi.org/10.1177/1073858414559409

Hilari, K., Byng, S., Lamping, D. L., & Smith, S. C. (2003). Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39): Evaluation of Acceptability, Reliability, and Validity. *Stroke*, *34*(8), 1944–1950. https://doi.org/10.1161/01.STR.0000081987.46660.ED

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: A review. *Clinical Neurophysiology Practice*, *2*, 19–25. https://doi.org/10.1016/j.cnp.2016.12.003

Richardson, J. D., & Dalton, S. G. (2016). Main concepts for three different discourse tasks in a large non-clinical sample. *Aphasiology*, *30*(1), 45–73. https://doi.org/10.1080/02687038.2015.1057891

Williams, L. S., Weinberger, M., Harris, L. E., Clark, D. O., & Biller, J. (1999). Development of a Stroke-Specific Quality of Life Scale. *Stroke*, *30*(7), 1362–1369. https://doi.org/10.1161/01.STR.30.7.1362