Study Protocol and Statistical Analysis Plan

Cerebellar Stimulation to Augment Chronic Aphasia Treatment

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1. Abstract

a. *Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.*

In this project, we will investigate the effects of cerebellar transcranial direct current (tDCS) stimulation during language therapy for naming in individuals with chronic aphasia (>6 months post stroke). Naming difficulties are a persistent and common symptom in aphasia after left-hemisphere (LH) stroke. Although the interventions to improve naming can have benefits (e.g., Hillis, 1998; Nickels, 2002; Raymer et al., 2007; Wisenburn & Mahoney, 2009), a massive number of treatment sessions is usually required to show gains, particularly in individuals with chronic, large LH stroke. Transcranial direct cortical stimulation (tDCS) is a promising adjunct to traditional SALT (Baker et al., 2010; Boggio et al., 2009; Ferrucci et al., 2008; Flöel et al., 2008; Fridriksson et al., 2011; Monti et al., 2008; 2013; Schlaug et al., 2008). tDCS is a safe, non-invasive, non-painful electrical stimulation of the brain which modulates cortical excitability by application of weak electrical currents in the form of direct current brain polarization (Weiss & Bikson, 2014). It is usually administered via saline-soaked surface sponge electrodes attached to the scalp and connected to a direct current stimulator with low intensities (Lang et al., 2005). Research paradigms employing tDCS are based on principles of neuroplasticity. Prior investigators have mainly focused on the role of LH in language recovery, wherein the electrode is placed in the left frontal or temporal region (e.g., Baker, Rorden, & Fridriksson, 2010; Fiori et al., 2011; Fridriksson et al., 2011; Vestito et al., 2014). However, in individuals with large lesions involving key language areas like the frontal and temporal cortex, it may be difficult to find viable tissue to stimulate in the LH. The question of whether right hemisphere (RH) facilitation is beneficial has been controversial considering that the recruitment of RH areas is frequently thought to be detrimental in the chronic stage. Several studies have shown benefit of RH C-tDCS or combined LH A-tDCS + RH C-tDCS (e.g., Floel et al., 2011; Jung et al., 2011; Marangolo et al., 2013). In addition, Naeser and colleagues have shown that the application of transcranial magnetic stimulation(TMS), suppressing the activation of the right Broca's homologue improved the performance of chronic, nonfluent participants with aphasia in noun naming (Martin et al., 2009; Naeser et al., 2011). However, inhibition of the RH might have detrimental effects on RH cognitive functions.
This study proposes a novel electrode placement for chronic stroke patients with aphasia with large LH lesions. Targeting the intact right cerebellum allows for the possibility of identifying a single target that can be used across groups of people with aphasia with varying lesion sites and size in the LH. Evidence from functional neuroimaging and clinical studies indicate that the right cerebellum is important for both language and cognitive functions (e.g., De Smet et al., 2013; Keren-Happuch et al., 2014; Murdoch, 2010; Schmahmann, 1991). In addition, cerebellar tDCS studies in healthy individuals provide evidence that right cerebellar tDCS modulates human cognitive and language functions (e.g., Boehringer et al., 2013;

Ferrucci et al., 2013; Macher et al., 2014; Pope & Miall, 2012). Importantly, the ability of cerebellar tDCS to modify behavior makes it an interesting therapeutic approach for post-stroke patients with aphasia.

Understanding the topography of network modulation is important to determine if there is reorganization of structure-function relationships following cerebellar tDCS. One way to determine the mechanism underlying improvement achieved with tDCS is by testing changes in the degree to which a targeted area is synchronized with other areas of the "language network", using resting state functional connectivity fMRI (rs-fMRI). Several studies have shown changes in connectivity that result from cerebellar tDCS using rs-fMRI in healthy controls, but have not demonstrated the specificity of the change in the cerebro-cerebellar network in stroke patients with aphasia, after tDCS versus sham.

This study will utilize a randomized, double-blind, sham controlled, within-subject crossover trial design. A random subset (half) of participants will be assigned to the "anode" group (Group Anode) and other half will be assigned to the 'cathode' group (Group Cathode). Participants will take part in 2 intervention periods of 15 computerized naming training sessions (3-5 sessions per week), with either tDCS + naming therapy or sham+ naming therapy, separated by 2 months. Detailed language evaluation will take place before, immediately after, 2 weeks and 2 months post-intervention for each condition.

2. Objectives

Primary Objective: The primary objective of this proposal is to determine whether anodal (A-tDCS) or cathodal (C-tDCS) right cerebellar tDCS along with naming therapy can improve naming outcome in individuals with chronic aphasia. This study will utilize a randomized, double-blind, sham controlled, within-subject crossover trial design. A random subset (half) of participants will receive A-tDCS +naming therapy and sham + naming therapy, and the other participants will receive C-tDCS + naming therapy and sham + naming therapy. Each group will receive 15 sessions of tDCS and 15 sessions sham stimulations (in randomized order), administered for the first 20 minutes of the one-hour treatment session of computerized naming treatment. Evaluation will take place before, immediately after, 2 weeks and 2 months post-intervention for each condition.

Aim: To determine whether tDCS to right cerebellum coupled with naming therapy will improve naming performance in participants with chronic post stroke aphasia more efficiently and for greater duration than naming alone (i.e., the sham condition). The primary outcome will be defined as the change in number of correctly named items on the Philadelphia Naming Test (PNT) (Walker & Schwartz, 2012) (pre-treatment and immediate post treatment testing). To assess change in naming ability, the primary outcome in this study, the PNT (plus a portion [N=80] of the trained items) will be administered before treatment starts and after treatment is completed. The change will be computed as the difference in the number of correctly named items pre-treatment PNT assessment to post-treatment PNT assessment.

Hypothesis 1a: Anodal tDCS (A-tDCS) or cathodal tDCS (C-tDCS) plus naming therapy will result in improved naming performance for trained and untrained items from baseline to post-treatment compared to sham plus naming therapy.
Hypothesis 1b. Improvement in naming performance for untrained items from baseline to 2 weeks and 2 month post treatment will be greater in both A-tDCS and C-tDCS +naming therapy conditions compared to the sham condition.
Hypothesis 1c. Combined tDCS and naming therapy will result in greater improvement in functional communication skills compared to sham plus naming therapy.

Statistical analysis: For **Aim 1, Hypothesis 1a,** each participant *i* will be treated either with tDCS (T) in the first period and sham (S) in the second period (in which case, we say $order_i$ = TS) or with sham in the first period and tDCS in the second period (in which case, we say $order_i$ = ST). For each participant *i*, we will measure the change in naming performance due to sham stimulation by subtracting naming accuracy before sham stimulation from that immediately after stimulation and will be denoted by δYi,sham. A similar measure will be computed for real tDCS stimulation, which will be denoted by δYi,tDCS. To evaluate the research hypothesis that the changes in naming performance under tDCS will on average be larger than the changes in naming performance under sham, we will analyze the data (order*i,* δYi,sham, δYi,tDCS), for participants $i = 1,\ldots,n$ to estimate the parameters of the standard crossover formulation. We will evaluate the predictive accuracy of 3 models: the model with only the tDCS vs. sham effect; the model that adds also the period effect and the model that adds also the interaction (carry-over effect); we will compare among the 3 models using the leave-one-out cross-validated R^2, which is an essentially unbiased way of comparing among such models. Then, we will estimate the tDCS vs. sham effect δ(T vs. S) using the model that explains the data best (highest R^2).

For Aim 1, Hypothesis 1b, Statistical analysis for this hypothesis will be the same as for hypothesis 1a but measuring changes at 2 weeks and 2 months respectively.

To examine the effect of condition (anode, cathode) on treatment outcome, a 2X4 ANOVA will be performed for both trained and untrained items, stimulation type (Anode tDCS, Cathode tDCS) and time (T1 (pre treatment), T2 (immediately post treatment), T3 (2 weeks follow up), and T4 (2 months follow up) as factors.

For Aim 1, Hypothesis 1c, change in functional communication skills will be analyzed by administering the ASHA Functional Assessment of Communication Skills for Adults (FACS) before and after treatment.

Power:

We expect to enroll 55 participants with aphasia over five years, and expect 45-50 will complete the study. This is based on data collected using IRB protocol number NA_00078932, PI Kyrana Tsapkini. T*he effect size for group anode was 0.6 for trained items and 1.5 for untrained items. The effect size for group cathode was 0.6 for trained items and 1.26 for untrained items.* We determined the number of participants to study, in order for the analysis to have 80% power to detect an effect size as low as 0.6 for both the anode and cathode group. Allowing for 10% attrition, a sample size of 55 was chosen (5 participants in group anode and 5 participants in group cathode each year). We predict no difficulty recruiting at least 10-15 APHASIC PARTICIPANTS each year as the Stroke Cognitive Outcomes and REcovery (SCORE) Lab (PI: Argye Hillis, MD) has recruited an average of 53 APHASIC PARTICIPANTS due to LH ischemic stroke each year in previous studies of aphasia recovery.

Secondary Objective:

Aim 2: To determine the topography of network modulation by right cerebellar tDCS in individuals with chronic aphasia by using resting-state fMRI. Functional connectivity in left hemisphere language regions are affected in stroke, including frontal, temporal and parietal areas. tDCS to a single region may alter functional connectivity within the whole network. This aim will investigate changes in functional connectivity patterns using resting state fMRI (rs-fMRI) at the local and network level induced by cerebellar tDCS plus computerized naming therapy compared to computerized naming therapy alone (sham).

Hypotheses:

2a. Combined tDCS and computerized naming therapy will result in changes in resting state connectivity between the right cerebellum and left (residual) language network in frontal, temporal and parietal regions and right homologues, compared to computerized naming therapy alone; and there will be connectivity

differences obtained with Anodal-tDCS (A-tDCS) vs Cathodal tDCS (C-tDCS).
2b. Combined tDCS and computerized naming therapy will result in changes in resting state connectivity within left (residual) and language network regions and right homologous regions, compared to language therapy alone; and there will be connectivity differences obtained with A-tDCS vs C-tDCS.
2c. Individuals who show the greatest change in naming untrained words will show the greatest change in connectivity between the cerebro-cerebellar network.

Statistical Analysis for Aim 2a. In analyzing rs-fMRI, the primary confirmatory metric of interest will be Fisher's Z transformations of correlations of regional average time courses. Prior to performing functional connectivity analysis, the rs-fMRI data will preprocessed and this will include spatial normalization to the standard MNI152 template, slice-timing correction, component based noise correction method (CompCor) 74 to control for correlations with heart rate, breathing, and motion correction. Lesion masking will be done prior to all statistical analysis. After preprocessing, ROI "seeds" will be used as masks to extract a mean time course for a seed for each patient. Time courses from a priori selected seed regions will extracted and then correlated. All correlations will be z-transformed using Fisher's r-to-z transformation for subsequent statistical analysis. Seed regions will be individually localized based on each subject's resting state data due to variation in lesion size and site. We will thus measure: the (ztransformed) correlation between target and left hemisphere ROI before the treatment and immediately after the treatment (tDCS and sham condition).

Statistical Analysis for Aim2b. Statistical analysis for this hypothesis will be the same as for hypothesis 1a but measuring the resting state connectivity between LH (residual) ROIs and RH ROIs.
To test the hypotheses that A-tDCS and C-tDCS modulate the language network in different ways, we will compare change in mean connectivity across specific ROIs that show the greatest change with tDCS in the anode group vs. the cathode group, using t-tests, with Bonferroni correction for multiple comparisons.
Statistical Analysis for Aim2c. This aim will test the hypothesis that individuals who show the greatest changes in naming untrained words will show the greatest changes in connectivity between the cerebro-cerebellar network. Because individual responsiveness to treatment will vary, as well as their lesion site and size, we will utilize an exploratory analysis to determine which region will show the greatest connectivity changes in individuals who show the greatest improvement in untrained items.

Aim 3: We will evaluate the effect of tDCS versus sham on change in lexical features of discourse based on the Cinderella story. The Cinderella story will be analyzed using the protocol, materials, transcription (CHAT) and the automated coding analysis (CLAN) systems through Aphasia Bank. Comparisons across conditions (tDCS vs sham) for change in lexical variability (nouns, verbs, and adjectives) will be evaluated.

Hypothesis: tDCS and naming therapy will result in greater improvement in discourse skills compared to sham plus naming therapy

Statistical Analysis: Change in discourse ability (based on the Cinderella story narration) will be analyzed by comparing change in lexical diversity for nouns, verbs and adjectives at the end of treatment compared with baseline using a t test.

3. Background (*briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)*

Introduction

Communication through language is central to the human experience. Disorders of language, such as post stroke aphasia, impede interaction and hamper interpersonal connections and reintegration into family life, work, and school (Wise, 2003). In the setting of post stroke aphasia, some degree of language recovery over time is common, mostly occurring within the first few months after stroke; however, severe and debilitating language deficits frequently persist, and decline in cognitive/language abilities and overall function can occur in those who do not receive speech and language therapy (SALT) (Dhamoon et al, 2012; Iadecola, 2013).

SALT is the mainstay of treatment for individuals with aphasia (Brady et al., 2012; Kurland et al., 2012). Clinicians strive to provide evidence-based interventions to improve language abilities after stroke. Meta-analyses indicate that about 100 hours of SALT are needed to significantly improve functional communication (Bhogal et al., 2003). Therapy is beneficial for language recovery in stroke, especially in the first three months post stroke (Hillis, 2010; Lazar et al., 2010); however, gains in therapy are variable and progress may be slow, especially in the chronic stage for patients with large lesions in the left hemisphere (Bhogal et al., 2003; Brady et al, 2012). Transcranial direct current stimulation (tDCS) is one method that has been proposed to boost behavioral language treatment in post stroke aphasia (Baker et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011; Jung et al., 2011; Marangolo et al., 2013; You et al., 2011). Although the precise mechanism of tDCS is still emerging (Weiss & Bikson, 2014), the prospect of augmenting the effectiveness of behavioral therapy is attractive to clinicians, patients, and their families and caregivers.

In the last 10 years, there has been an increased interest in using tDCS to modulate cognitive functions in healthy individuals as well as in individuals with various disorders. In addition to its appeal as an effective adjunctive intervention, there are several reasons for this increased interest in tDCS research. One reason pertains to safety considerations: tDCS seems to have no significant adverse side effects, provided that stimulation parameters are kept within safety limits (see Nitsche et al., 2008; Poreisz et al., 2007). In a meta-analysis study, the most common adverse sensation was mild tingling and mild itching under the electrodes and seldom-occurring headache, fatigue, and nausea (Poreisz et al., 2007). Furthermore, tDCS is not reported to provoke seizures and current tDCS protocols are not found to induce brain edema or changes in the blood brain barrier (Nitsche et al., 2004). A second benefit of tDCS pertains to portability and cost. The tDCS apparatus is more portable, less expensive, and easier to use than other technologies, like transcranial magnetic stimulation (TMS). These features allow treatment to be delivered not only in clinical settings, but also in a patient's own home. Third, tDCS allows one to easily conduct placebo (sham) stimulation-controlled studies, because, with the exception of a slight itching and mild tingling sensation, participants rarely experience sensations related to the stimulation. A method to blind participants as to whether they are receiving real or sham tDCS in a research treatment protocol is turn the tDCS stimulator on for 30 seconds at the start of the sham condition to induce scalp sensations associated with stimulation, and then gradually decrease and turn off tDCS within the next 15 seconds (Gandiga et al., 2006). Finally, tDCS is also well suited to neuromodulation concurrent with behavioral SALT. For example, Broca's area (inferior frontal cortex) can be easily and comfortably targeted with tDCS along with behavioral treatment for naming.

Mechanism of tDCS

Cathodal polarization is thought to decrease cortical excitability due to hyperpolarization of cortical neurons; whereas, anodal polarization increases cortical excitability due to subthreshold depolarization (Bindman et al., 1962; Creutzfeldt et al., 1962; Gomez Palacio Schjetnan et al., 2013). The brain

mechanisms that induce the aftereffects of tDCS are thought to be N-methyl-D-aspartate (NMDA) receptor-dependent and calcium channel activity (Nitsche et al., 2003), and share similarities with long-term potentiation and depression, which are critical in synaptic plasticity, a cellular mechanism for learning and memory (Monte-Silva et al., 2013; Rioult-Pedotti et al., 2000). tDCS induces neuroplasticity by subthreshold neuronal membrane resting potential modification through application of direct currents, and the aftereffects are NMDA receptor-dependent. Nitsche and Paulus (2001) showed for the first time that weak tDCS is capable of inducing tDCS duration-dependent, long-lasting cerebral excitability elevations in humans. tDCS does not generate action potentials; moreover, it is site-specific, but not site-limited, meaning that it affects not only the targeted site, but related cortical areas as well.

tDCS in Aphasia Research

Aphasia is one of the leading causes of disability following stroke. Anomia or difficulty with naming is the most common deficit in individuals with aphasia. Although the interventions to improve naming can have benefits (Hillis, 1998; Kiran & Thompson, 2003; Nickels, 2002; Raymer et al., 2007; Wisenburn & Mahoney, 2009) a massive number of treatment sessions is usually required to show gains, particularly in individuals with chronic large LH stroke. There is evidence that tDCS may be useful for enhancing the effects of behavioral aphasia treatment. Accumulating evidence indicates that anodal tDCS LH language regions has the potential to augment language outcomes in individuals with chronic aphasia. Prior investigators have mainly focused on the role of LH in language recovery, wherein the electrode is placed in the left frontal or temporal region (e.g., Baker, Rorden, & Fridriksson, 2010; Fiori et al., 2011; Fridriksson et al., 2011; Vestito et al., 2014). However, in individuals with large LH stroke, improvement of language functions that are dependent on LH networks proves to be difficult. In such cases, some investigators have investigated enhancing the function of non-damaged hemisphere with the goal of facilitating compensation. The question of whether right hemisphere (RH) facilitation is beneficial has been controversial considering that the recruitment of RH areas is frequently thought to be maladaptive in the chronic stage. Several studies have shown benefit of RH Cathodal tDCS or combined LH Anodal tDCS + RH Cathodal-tDCS (Floel et al., 2011; Jung et al., 2011; Kang et al., 2011; Marangolo et al., 2013).
In addition, Naeser and colleagues have shown that the application of rTMS, suppressing the activation of the right Broca's homologue improved the performance of chronic, nonfluent participants with aphasia in noun naming (Martin et al., 2009, Naeser et al., 2005, 2011). This study proposes a novel electrode placement for chronic stroke patients with aphasia with large LH lesions. Targeting the intact right cerebellum allows for the possibility of identifying a single target that can be used across groups of people with aphasia with varying lesion sites and size in the LH.

Cerebellar tDCS

Current evidence derived from detailed neuroanatomical investigations and functional neuroimaging studies suggests that the right cerebellum has a cardinal role in various aspects of cognitive processing including language processing (e.g., Stoodely, Valera, & Schmahmann, 2012, De Smet et al., 2013; Keren-Happuch, et al., 2014; Marien et al., 2014). Damage to the right cerebellum has been associated with deficits in language tasks such as verbal fluency, naming, word generation, word stem completion, and syntactic processing (e.g., Gomez et al., 1997; Marien et al., 2001; Richter et al., 2007; Baillieux et al., 2010). fMRI results reveal robust activation in the right cerebellum in participants with aphasia with varying lesion site and size from the acute stage to the chronic stage during a picture-naming task, a task similar to that employed in the current study. The cerebellum is massively interconnected with the cerebral cortex, and neuroanatomical studies have shown bidirectional pathways between the cerebellum and multiple cortical structures involved in cognitive processing. More specifically, the cortex sends information to the

cerebellum via pontine nuclei, while the cerebellum sends information back to the cortical areas through dentatothalamic pathways (Middleton & Strick, 1994; Murdoch, 2010). Cerebellar-tDCS techniques are gaining popularity because the areas involved in cognitive processing are most accessible to tDCS, and the procedure is relatively inexpensive and easy to perform (Ferrucci & Priori, 2014; Grimaldi et al., 2014; Priori et al., 2014). Anodal stimulation has an excitatory effect and increases the output of Purkinje cells, which may increase inhibition of the facilitatory pathway from the cerebellar nuclei to cerebral cortex. Cathodal stimulation has an opposite effect, i.e., dis-inhibition of the cerebral cortex by reducing Purkinje cell inhibition of the cerebellar nuclei (Galea et al., 2009). Beneficial cognitive effects from right cerebellar tDCS have been found for both anodal and cathodal stimulation. For example, in a study of verb generation in healthy individuals, C-tDCS applied over the right cerebellum facilitated performance on the verb generation task, as compared to A-tDCS and sham tDCS (Pope & Miall, 2012). Another study conducted with healthy individuals on the influence of C-tDCS on verbal working memory, as measured by forward and backward digit span, found that C-tDCS reduced forward digit spans and blocked the practice-dependent increase in backward digit spans (Ferrucci et al., 2008). Similarly, A- tDCS to the right cerebellum improved implicit learning in healthy subjects compared to sham (Ferrucci et al., 2013). The results from these studies are very important not only because they inform us about the role of the cerebellum in different cognitive tasks, but also because they suggest that direct current stimulation over the cerebellum can modulate behavior in healthy individuals. The ability of cerebellar tDCS to modify behavior makes it an interesting approach with a potential therapeutic role for individuals with aphasia.

Several studies have harnessed resting state-fMRI to investigate the human cerebellum, providing insight into cerebellar-cortical interactions in healthy controls (Allen et al., 2005; Habas et al., 2009; O'Reily et al., 2009; Turkeltaub et al., 2016). While these studies indicate that there are differences in cortical resting state brain networks before and after tDCS in healthy individuals, the effects of language augmentation induced by cerebellar tDCS have not yet been evaluated in participants with aphasia. If tDCS induces synaptic connectivity changes, then multiple repetitive cerebellar tDCS sessions may alter (perhaps normalize to some degree) the functional connectivity between nodes of the language network in aphasia. Investigating resting state functional connectivity will provide key insight into the neural mechanisms underlying polarity-specific changes in the network dynamics induced by cerebellar tDCS. This may aid in determining predictors of treatment outcome for anodal and cathodal tDCS, in order to provide more effective targeted treatment for people with aphasia.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Procedures Overview

Study design overview: Participants will take part in 2 intervention periods of 15 training sessions (3-5 per week), with either tDCS + behavioral language therapy or sham+ behavioral language therapy, separated by 2 months. A computer-delivered naming treatment will be coupled with the stimulation. The computer-delivered treatment task will be 45-minutes in total length, so that it will commence at the same time as the tDCS administration and continue for another 25-minutes after the tDCS has ceased.

Participants who agree to participate in the MRI portion of the study (and have none of the additional exclusion criteria for MRI) will have structural and resting state MRI prior to start of Phase 1 intervention, end of Phase intervention 1, prior to start of Phase 2 intervention, and end of Phase 2 intervention.

In order to minimize the need for research-only in-person visits, telemedicine visits will be substituted for portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. For the current study, we will utilize telemedicine visits when appropriate for consenting and for all the assessments visits (visits 1 & 2, 19-21, 37-39). Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Visit 1: During the first visit, participants will sign informed consent and under go screening assessments. This will include tDCS and MRI safety screening. Neurological examination will also be performed (see below).

Visit 2: This involves detailed language testing (see below) including computerized naming assessments. This will be the baseline language testing. A screening task will be administered prior to the baseline language testing. Participants must achieve at least 65% accuracy on screening task (comparable to treatment task) on 1 of 3 attempts. The screening test is administered to ensure that the participant understands the treatment task requirement. The probability that a patient will achieve >65% accuracy by chance on each of the three tries is low: $p<0.05$. If a participant is unable to reach this level of accuracy, study enrollment will be discontinued. The Philadelphia Naming Test (PNT) is a computerized naming test. PNT is part of the baseline language testing. Participants who's correct naming score exceeds an average of 140/175 (greater than 80% accuracy) on the PNT baseline session will be excluded to leave at least a 20% improvement margin. That is, participants who already score close to ceiling may have limited room for naming improvement as measured by the PNT.

Visit 3: Participants may be asked to get structural MRI (to determine site of lesion) and function fMRI (resting state). If participant doesn't not have a lesion in the right cerebellum, participant will be able to start intervention. This visit is only for participants who consent to MRI and have no contraindication.

Visit 4-18: This will involve the treatment sessions for the first intervention period. Prior to the start of treatment, participants will be randomly assigned to Group Anode or Group Cathode. Within each group, each participant will be randomly assigned to receive either " tDCS then sham" or "sham then tDCS". For example, if a participant is randomly assigned to received "tDCS then sham", the first intervention period of 15 sessions will be tDCS+ computerized naming treatment and the second intervention period will be 15 sessions of sham + computerized naming treatment.

Visit 19: This visit will involve post treatment language testing and MRI. This visit will be similar to Visit 3.
Visit 20: The will be the 2 week post treatment follow up language testing visit (Similar to Visit 3 and 19).

Visit 21: 2 month follow up visit. This will be considered as baseline testing for phase 2 intervention. MRI will also be obtained
Visit 22-36: This will involve the treatment sessions for the second intervention period. The opposite tDCS condition will be implemented here. For example, if a participant is randomly assigned to received "tDCS then sham", the second intervention period will be 15 sessions of sham + computerized naming treatment.
Visit 37: This visit will involve post treatment language testing and MRI.
Visit 38: 2 week follow up language testing after second intervention period.
Visit 39: 2 month follow up language testing after second intervention period.

Procedures for Screening (Visit 1)

The following procedures will be performed:

1. Obtain written informed consent: A signed and dated informed consent form will be obtained from each participant before conducting any screening procedures. Participants will be then be assigned a temporary identification number for the purposes of initial screening.
   All research staff authorized to obtain informed consent will have completed the Miami CITI course in the Responsible Conduct of Research and Protection of Human Subjects prior to their involvement with the study. Furthermore, they will be oriented to the study and trained by the study PI and study co-investigators who have all had extensive training and experience in the ethical and practical aspects of informed consent procedures.
2. Administer the tDCS safety screening and MRI safety screening
3. Review inclusion/exclusion criteria.
4. Obtain medical history.
5. Conduct neurological examination.

Procedures for language testing (Visit 2)
Participants will first complete a screening task. This is administered to verify that participants comprehend task requirements. Participants must achieve at least 65% accuracy on screening task (comparable to treatment task) on 1 of 3 attempts to be able to participate in the treatment. If a participant is unable to reach this level of accuracy, study enrollment will be discontinued.

Procedure for MRI (Visit 3) .For all participants who consent to MRI and have no contraindication. Participants will receive structural MRI scanning to determine site of lesion and Resting State Functional Connectivity fMRI

The following language tests will be administered on Visit 2

1. Administer the Boston Diagnostic Aphasia Examination (BDAE) Short form: The Boston Diagnostic Aphasia Examination is a comprehensive, multifactorial battery designed to evaluate a broad range of language impairments that often arise as a consequence of organic brain dysfunction. The examination is designed to go beyond simple functional definitions of aphasia into the components of language dysfunctions (symptoms) that have been shown to underlie the various aphasic syndromes. Thus, this test evaluates various perceptual modalities (e.g., auditory, visual, and gestural), processing functions (e.g., comprehension, analysis, problem-solving), and response modalities (e.g., writing, articulation, and manipulation). This approach allows for the neuropsychological analysis and measurement of language-

related skills and abilities from both ideographic and nomothetic bases, as well as a comprehensive approach to the symptom configurations that relate to neuropathologic conditions. The short form uses selected items from each of the tests and is takes about 60 minutes to administer.

2. Administer the Boston Naming Test-Second Edition (BNT): The BNT represents a measure of object naming abilities from a corpus of 60 line drawings. Object names are ranked along a continuum, with easier, more high frequency words appearing at the beginning of the test and more difficult, lower-frequency words appearing near the end. To eliminate participant frustration, the BNT implements a ceiling effect so that once the participant incorrectly names eight items in a row, testing will cease, with the assumption that (s)he would not correctly name the upcoming, more difficult words (Kaplan et al., 2001). SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 5-20 minutes.

3. Administer the Apraxia of Speech Rating Scale (Strand et al., 2014), to rate frequency and severity of particular characteristics of apraxia of speech (AOS): The Apraxia of Speech Rating Scale is a rating scale, in which speech characteristics are evaluated in terms of frequency and severity. Higher scores indicate more severe apraxia of speech. SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-15 minutes.

4. Administer the Pyramids and Palm Trees Test (PPTT) (Short form): The PPTT is a test of semantic processing. This test assesses the degree to which a participant can access meaning from pictures. Information from the test will help determine whether a participant's difficulty in naming or pointing to a named picture is due to a difficulty in retrieving semantic information from pictures (Howard & Patterson, 1992; Breining et al, 2014). SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-20 minutes.

5. Administer the ASHA Functional Assessment of Communication Skills for Adults (FACS). This is a tool used for measuring and recording the functional communication of adults with speech, language, and cognitive communication disorders. This assessment is comprised of 43 items and assesses functional communication in four areas: social communication; communication of basic needs; reading, writing, and number concepts; and daily planning.

6. Administer Computerized Philadelphia Naming Test (see section below on Computerized Naming Assessments): This test is administered to determine generalization from trained to untrained items. This test is a 175-item picture naming test for the psycholinguistic exploration of lexical access in nonaphasic and aphasic speakers. Items are line-drawn exemplars of animate and inanimate objects (all non-unique, i.e., no famous people or landmarks). Participants whose correct naming score exceeds an average of 140/175 on the PNT baseline sessions will be excluded to leave at least a 20% improvement margin. That is, patients who already score close to ceiling may have limited room for naming improvement as measured by the PNT.

7. Administered trained item assessment naming task (see section below on Computerized Naming Assessments). This name task is administered to determine whether the participant's ability to name the trained items improved over the course of treatment. This consists of the 80 pictures that are all nouns.

8. Administer the Cinderella story: See procedure below.

9. Procedures for the Computerized Naming Assessments (Visit 2, 19, 20, and corresponding baseline and follow-up evaluations for each treatment period)

1. Turn on the laptop computer and position in front of the participant.
2. Set up and start internal web-camera for audio-visual recording. Administer the PNT and trained naming assessment on a laptop computer. Instruct the participant to overtly name each picture as soon as it is displayed. Trials will end following a response or after 20-seconds have elapsed, in which the administrator will say the correct picture name in order to discourage perseveration on subsequent trials.
3. Stop web-camera and save video file for later scoring of naming.

Procedures for the "Cinderella Story" Picture Discourse Analysis (Visit 2, 19, 20, and corresponding baseline and follow-up evaluations for each treatment period)

1. The Cinderella story is to be completed following the administration of the PNT, so the laptop computer and web-camera set-up will need to remain for this portion of the assessment.
2. Place the picture book in front of the participant.
3. Tell the participant, "I'm going to ask you to tell a story. Have you ever heard the story of Cinderella?" (Make note of answer) "Do you remember much about it? These pictures might remind you of how it goes. Take a look at the pictures and then I'll put the book away, and ask you to tell me the story in your own words." Allow the participant to look through the book (assist with page turning, if needed) and then, if necessary, prompt: "Now tell me as much of the story of Cinderella as you can. You can use any details you know about the story, as well as the pictures you just looked at." Continue until the participant concludes the story or it is clear s/he has finished.
4. Stop web-camera and save video file for later transcription.

Procedures for Treatment (Visit 4-18) for intervention period 1 and Visits 22-36 for intervention period 2

The following procedures will be performed:

1. Measure the electrode location on the scalp (Right cerebellum: 1 cm below the inion and 4 cm lateral)
2. Soak the 2 sponge electrodes in saline solution and place inside rubber electrode holders.
3. Place the anode electrode (Group Anode) under the designated area on the right cerebellum located during the electrode positioning process (marked with a star) and reference electrode (cathode in Group Anode) on the right deltoid muscle. This configuration will be reversed in Group Cathode.
4. Connect the electrode cables to the Soterix tDCS device.
5. Start the tDCS device and enter the code. Soterix clinical trial tDCS device includes a software for true operator blinding where the PI can have preset codes for tDCS and sham trials including the dosage and the clinician will enter the codes and the device will present either tDCS or sham depending on the code that was assigned.
6. Set-up the computer-delivered naming task: Turn on computer and position in front of participant. Plug in the red/green response buttons into the computer and position in front of participant. Plug in the ear bud headphones into the computer and place in participant's ears. Play example sound clip to verify with participant that sound is sufficient; if sound is not sufficient, adjust volume until participant is satisfied. Locate the participant's designated treatment folder and open.
7. Instruct the participant how to perform the self-administered computer-delivered naming treatment, consisting of a picture/seen and heard spoken word verification task, which will be coupled with the stimulation. The computerized treatment task will be 45-minutes in total length, so that it will commence

at the same time as the tDCS administration. A picture will be presented for 2 s on a laptop computer screen and will be immediately followed by an audio-visual display of a female speaker's mouth saying a noun. Video of the speaker producing the noun is presented in synchrony with the audio via in-ear headphones. The spoken word either will or will not match the preceding picture. In the event of a match, instruct the participant to press a large green response button interfaced with the computer, and in the case of a non-match, instruct the participant to press a red button. Half of the picture/word pairs will match, while the other half will not. The computer will provide immediate visual feedback following a response in the form of a "smiley face" for correct answers and a "frowny face" for incorrect answers. Additionally, following the completion of a treatment session, a data file of the participant's responses will be automatically saved, and the accuracy score from that session will be displayed on the computer screen.

8. "Click" on the START icon on the "tDCS device" to simultaneously start stimulation and the computer treatment task.
9. Record any Adverse Events experienced during the treatment session or since the last visit on the AE log.
10. Assess and record the participant's comfort rating using the Wong-Baker FACES Pain Rating (Wong & Baker, 1988) Scale following treatment completion.

Procedures for Neurological Examination (Visits 1)
All participants will be monitored closely for safety and neurological functioning during the duration of the study. In addition to the comfort ratings recorded daily a neurological examination will be administered during Visit 1. If there is any change noted in the neurological status by the clinician during the duration of the study, then Dr. Hillis will be notified and the neurological examination will be repeated.

Procedure for tDCS stimulation

The following procedures will be performed:

1. Measure the electrode location on the scalp (Right cerebellum: 1 cm below the inion and 4 cm lateral).
2. Soak the 2 sponge electrodes in saline solution and place inside rubber electrode holders.
3. Place the anode electrode (Group Anode) under the designated area on the right cerebellum located during the electrode positioning process (marked with a star) and reference electrode (cathode in Group Anode) on the right deltoid muscle. This configuration will be reversed in Group Cathode.
4. Connect the electrode cables to the Soterix tDCS device.
5. Start the tDCS device and enter the code. Soterix clinical trial tDCS device includes a software for true operator blinding where the PI can have preset codes for tDCS and sham trials including the dosage and the clinician will enter the codes and the device will present either tDCS or sham depending on the code that was assigned.

b. Study duration and number of study visits required of research participants.

Participants will receive treatment for 3-5 weeks (3-5 sessions in a week: total 15 sessions) for each of the intervention period. There will be 1 tDCS treatment period and 1 sham treatment period for each participant. We will follow-up the participants with 2-week and 2-month follow-up sessions after each treatment period. Study duration will be approximately 6 months and the number of visits for each participant will be 39.

Table 1: An example of the time course of stimulations (each stimulation period encompassing 15 stimulation sessions, 3-5 per week) and subsequent evaluations.

Group	Visit 1	Visit 2	Visit 3	Visit 4-18	Visit 19	Visit 20	Visit 21	Visit 22-36	Visit 37	Visit 39	Visit 39
Grope Anode	Screening	Language assessment	MRI Structural and functional	15 tx sessions (tDCS or sham)	Post tx testing and MRI	2 week follow up testing	2 month follow up testing. Also language assessment for 2nd intervention period. MRI	15 tx sessions (sham or tDCS)	Post tx Testing and MRI	2 week follow up testing	2 month follow up testing.
Grope Cathode	Screening	Language assessment	MRI Structural and functional	15 tx sessions (tDCS or sham)	Post tx testing and MRI	2 week follow up testing	2 month follow up testing. Also language assessment for 2nd intervention period. MRI	15 tx sessions (sham or tDCS)	Post tx Testing and MRI	2 week follow up testing	2 month follow up testing.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Randomization and Blinding

The study is to be conducted in a double-blind manner. The subjects and the clinician, and the clinical staff involved in this study will not know the treatment assignment. Participant codes are programed into the tDCS device so that the clinician administering the treatment only needs to enter the code to start stimulation without knowing whether those specific numbers are associated with tDCS or Sham. The PI will have access to the unblinded list of randomization codes and treatment assignments.

d. Justification of why participants will not receive routine care or will have current therapy stopped

Participation in this study will not disrupt any current care or therapy.

e. Justification for inclusion of a placebo or non-treatment group

All participants will be participants who will undergo active and sham conditions, thus serving as their own control.

f. Definition of treatment failure or participant removal criteria

Participants will be removed from the study if they are unable to comply with task instructions or tolerate the tDCS procedure.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely

When the study ends participants will continue to receive management with Dr. Hillis or their own neurologist as usual (generally follow-up visits every about 6). If a patient's participation in the study ends prematurely s/he will still receive care as before. In sum, termination of the study or termination of participation in it will not affect regular therapy he or she may be receiving.

Changes to Procedures in the Event of a Pandemic

We will take several precautions to minimize the risk of exposure to COVID-19 for our participants as well as for members of our research team. We will rely on these same contingencies in the event of another pandemic.

- In order to minimize the need for research-only in-person visits, telemedicine visits will be substituted for portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. For the current study, we will utilize telemedicine visits when appropriate for consenting and for all the assessments visits (visits 1 & 2, 19-21, 37-39). Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

- In person visits will be conducted in the PI research lab or at the participant's home. We will follow Johns Hopkins University guidelines. We will perform in person visits in the PI's lab or home visits (preferably outdoors, e.g. on a porch if privacy is not an issue) to limit contact of participants with others at the hospital setting.

- Prior to each scheduled visit, we will call the participant and screen for COVID-19 symptoms and exposure. Screening will occur at the time of scheduling and the day prior to the scheduled session. If a participant reports exposure or symptoms, the visit will be cancelled and rescheduled as appropriate.

- Research team members will reference JHU policies for self-screening and will defer any in-person activities if they suspect that they have any active COVID-19 symptoms. Another research team member will conduct the scheduled session if possible, or the session will be cancelled and rescheduled as appropriate.
- Equipment and work surfaces will be disinfected prior to and after each session.

- We will ask caregivers/family/friends of participants not to attend treatment sessions with participants in order to reduce the number of people in close contact.

- Research lab members will wear a surgical mask, face shield, and gloves during in person sessions. Participants will also be asked to wear a mask for the session, and if they do not have a mask, one will be provided for them.

- Participants and research team members will be asked to use hand hygiene at the beginning of in-person test sessions before handling testing equipment; this may include washing hands with soap and water or using hand sanitizing gel/foam approved by the university.
- We will follow Johns Hopkins University guidelines to limit the number of research team members conducting in person visits with participants. One study team member will conduct the treatment/assessment. We will also limit the number of research team members to one person present in each room of the lab at any given time.

5. Inclusion/Exclusion Criteria

Participants in this study will have stroke-induced aphasia. Diagnostic evaluations will be conducted during the participants' initial visit to confirm aphasia diagnosis.

Participant Inclusion Criteria

Participants must satisfy the following inclusion criteria to be considered eligible for entry into this study:

1. Participants must have sustained a left hemisphere stroke.
2. Participants must be fluent speakers of English by self-report.
3. Participants must be capable of giving informed consent or indicating another to provide informed consent.
4. Participants must be age 18 or older.
5. Participants must be premorbidly right handed.
6. Participants must be at least 6 months out from the stroke of interest
7. Participants must have an aphasia diagnosis as confirmed by the Boston Diagnostic Aphasia Examination (BDAE) Short Form.
8. Participants must achieve at least 65% accuracy on screening task (comparable to treatment task) on 1 of 3 attempts

Participant Exclusion Criteria

Participants with any of the following characteristics will not be eligible for entry into this study:

1. Participants with lesion involving the right cerebellum
2. Previous neurological or psychiatric disease.
3. Seizures during the previous 12 months.
4. Uncorrected visual loss or hearing loss by self-report.
5. Use of medications that lower the seizure threshold (e.g., methylphenidate, amphetamine salts).
6. Use of NMDA antagonists (e.g., memantine).
7 > 80% correct responses on the PNT at baseline.
8. History of brain surgery or any metal in the head.
9. Scalp sensitivity (per participant report).

6. Drugs/Substances/Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

tDCS has been established as a valid and reliable tool for at least temporarily affecting brain and behavior with minimal risks. Stimulation will be delivered by a battery-driven constant current stimulator (Soterix device, or a comparable model). The stimulator is not connected to a mainline power source and cannot

produce in excess of 4mA of current. We will use non-metallic, conductive rubber electrodes covered by saline-soaked sponges to minimize the potential for chemical reactions at the interface of the scalp or skin and the electrodes.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. N/A

7. Study Statistics

a. Primary outcome variable

The primary outcome will be defined as the change in number of correctly named items on the PNT (pre-treatment and immediate post-testing). To assess change in naming ability, the primary outcome in this study, the PNT (plus a portion [N=80] of the trained items) will be administered.

b. Secondary outcome variables

We will evaluate the effect of tDCS versus sham on change in lexical features of discourse based on the Cinderella story. The Cinderella story will be analyzed using the protocol, materials, transcription (CHAT) and the automated coding analysis (CLAN) systems through Aphasia Bank.

c. Statistical plan including sample size justification and interim data analysis

Statistical Analysis

The primary hypothesis is that tDCS over a targeted region combined with computer-delivered SALT is associated with greater gains in accuracy in naming pictures, compared to sham combined with the same computer-delivered SALT in post stroke aphasia.

For **Aim 1, Hypothesis 1a,** each participant *i* will be treated either with tDCS (T) in the first period and sham (S) in the second period (in which case, we say $order_i$ = TS) or with sham in the first period and tDCS in the second period (in which case, we say $order_i$ = ST). For each participant *i*, we will measure the change in naming performance due to sham stimulation by subtracting naming accuracy before sham stimulation from that immediately after stimulation and will be denoted by δYi,sham. A similar measure will be computed for real tDCS stimulation, which will be denoted by δYi,tDCS. To evaluate the research hypothesis that the changes in naming performance under tDCS will on average be larger than the changes in naming performance under sham, we will analyze the data (order*i,* δYi,sham, δYi,tDCS), for participants $i = 1,\ldots,n$ to estimate the parameters of the standard crossover formulation. We will evaluate the predictive accuracy of 3 models: the model with only the tDCS vs. sham effect; the model that adds also the period effect and the model that adds also the interaction (carry-over effect); we will compare among the 3 models using the leave-one-out cross-validated R^2, which is an essentially unbiased way of comparing among such models. Then, we will estimate the tDCS vs. sham effect δ(T vs. S) using the model that explains the data best (highest R^2).

For Aim 1, Hypothesis 1b, Statistical analysis for this hypothesis will be the same as for hypothesis 1a but measuring changes at 2 weeks and 2 months respectively.

To examine the effect of condition (anode, cathode) on treatment outcome, a 2X4 ANOVA will be

performed for both trained and untrained items, stimulation type (Anode tDCS, Cathode tDCS) and time (T1 (pre treatment), T2 (immediately post treatment), T3 (2 weeks follow up), and T4 (2 months follow up) as factors.
For Aim 1, Hypothesis 1c, change in functional communication skills will be analyzed by administering the ASHA FACS scale before and after treatment.

The secondary objective 1 will test the hypotheses that combined tDCS and naming therapy will change functional connectivity between the target region (right cerebellum) and undamaged cortical regions of interest (ROI) in the LH language network, compared to language therapy alone (sham); and there will be differences obtained with anodal vs cathodal tDCS. The right cerebellar ROI will include the right lateral cerebellum.
Statistical Analysis for Aim 2a. In analyzing rs-fMRI, the primary confirmatory metric of interest will be Fisher's Z transformations of correlations of regional average time courses. Prior to performing functional connectivity analysis, the rs-fMRI data will preprocessed and this will include spatial normalization to the standard MNI152 template, slice-timing correction, component based noise correction method (CompCor) 74 to control for correlations with heart rate, breathing, and motion correction. Lesion masking will be done prior to all statistical analysis. After preprocessing, ROI "seeds" will be used as masks to extract a mean time course for a seed for each patient. Time courses from a priori selected seed regions will extracted and then correlated. All correlations will be z-transformed using Fisher's r-to-z transformation for subsequent statistical analysis. Seed regions will be individually localized based on each subject's resting state data due to variation in lesion size and site. We will thus measure: the (ztransformed) correlation between target and left hemisphere ROI before the treatment and immediately after the treatment (tDCS and sham condition).

Statistical Analysis for Aim2b. Statistical analysis for this hypothesis will be the same as for hypothesis 1a but measuring the resting state connectivity between LH (residual) ROIs and RH ROIs. To test the hypotheses that A-tDCS and C-tDCS modulate the language network in different ways, we will compare change in mean connectivity across specific ROIs that show the greatest change with tDCS in the anode group vs. the cathode group, using t-tests, with Bonferroni correction for multiple comparisons.
Statistical Analysis for Aim2c. This aim will test the hypothesis that individuals who show the greatest changes in naming untrained words will show the greatest changes in connectivity between the cerebro-cerebellar network. Because individual responsiveness to treatment will vary, as well as their lesion site and size, we will utilize an exploratory analysis to determine which region will show the greatest

Secondary objective 2 will test the hypothesis that tDCS and naming therapy will result in greater improvement in discourse skills compared to sham plus naming therapy

Statistical Analysis: Change in discourse ability (based on the Cinderella story narration) will be analyzed by comparing change in lexical diversity for nouns, verbs and adjectives at the end of treatment compared with baseline using a t test.

Sample Size Determination

We expect to enroll 55 participants with Aphasia over five years, and expect 45-50 will complete the study. This is based on data collected using IRB protocol number NA_00078932, PI Kyrana Tsapkini. T*he effect size for group anode was 0.6 for trained items and 1.5 for untrained items. The effect size for group cathode was 0.6 for trained items and 1.26 for untrained items.* We determined the number of participants to study, in order for the analysis to have 80% power to detect an effect size as low as 0.6 for both the anode and cathode group. Allowing for 10% attrition, a sample size of 55 was chosen (5 participants in group anode and 5 participants in group cathode each year). We predict no difficulty recruiting at least 10-15 APHASIC PARTICIPANTS each year as the Stroke Cognitive Outcomes and REcovery (SCORE) Lab (PI: Argye Hillis, MD) has recruited an average of 53 APHASIC PARTICIPANTS due to LH ischemic stroke each year in previous studies of aphasia recovery.

Missing Data

We plan to minimize this by avoiding prolonged intervals between stimulations: 2 months may seem long with regard to the literature, but it is a reasonable length of time to be able to determine sustainability of any therapy. To minimize possible biases, analyses will be by intention to treat; any missing data will be addressed with the technique of multiple imputation (Ball et al., 2002; Rubin, 2009), generally recognized as best for handling missing data (Little et al., 2012).

Secondary Analyses

In addition to the primary outcome, secondary analyses will be conducted. We will examine changes in types of naming errors (defined by the PNT) by tDCS treatment group. The Cinderella story will be analyzed by comparing lexical diversity (VOCD) for nouns, verbs and adjectives; number and types of errors; length and patterns of pauses by treatment group. Pre and post comparisons with both non-aphasic and aphasic speakers from the Aphasia Bank database who share a number of demographic features (e.g., type and severity of aphasia, age, etc.) will also be made.

At the end of the study, for the interval scale variables, mean change from baseline to immediate post-testing in secondary outcome measures will be reported by treatment group along with the 95% confidence intervals. Treatment comparisons will be made with a paired t- test. For binary variables, the proportion of subjects immediately post-testing will be reported by treatment group along with the 95% confidence intervals.

d. Early stopping rules. N/A

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

tDCS

The present study involves application of transcranial direct current stimulation. Weak direct currents can be applied non-invasively, transcranially and painlessly (Nitsche et al., 2003; Priori et al., 2009). This is a non-invasive and painless technique that leads to transient changes in cortical excitability that are fully reversible (Nitsche et al., 2002). There are no known risks of tDCS to other than mild local discomfort at the electrode sites (much less than TMS for example). Several published studies on humans (Boggio et al., 2009; Gandiga et al., 2006; Hummel et al., 2005; Nitsche et al., 2003; 2004; Paulus, 2003; Uy & Ridding, 2003) reported the following objective safety data:

- No heating of electrodes
- No demonstrable changes in the skin underlying electrode placement after a stimulation period similar to the one proposed in this protocol.
- Mild itching sensation in the absence of pain that never led to stopping a study.
- No change in serum neuron-specific enolase (NSE, marker for neuronal damage) in 5 participants immediately and 1 hour after exposure to 13 min of 1 mA anodal tDCS to motor cortex
- No changes in diffusion weighted or contrast-enhanced MRI and in EEG after exposure to tDCS (Nitsche et al., 2004).

Two reports, one evaluating the safety of tDCS applied in different brain regions in 102 healthy and stroke individuals (Poreisz et al., 2007) and another one investigating the safety of different forms and intensities of tDCS in 103 healthy participants (Iyer et al., 2005), concluded that tDCS is safe and only associated with relatively minor adverse effects in healthy and participants with different neurological conditions. In addition, a double-blind sham-controlled study has shown that comparing tDCS and sham stimulation of the motor cortex elicited minimal discomfort and difference in the duration of tingling sensations. There were no differences in self-rated attention or fatigue, and the study participants or investigators could not distinguish real tDCS from sham (Gandiga et al., 2006). Taken together, all available research suggests that prolonged application should not pose a risk of brain damage when applied according to safety guidelines.

MRI
Participants may undergo MRI scanning in the present study. The effects of undergoing MR scanning have been extensively studied and there are no risks associated with an MR exam. The patient may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. They will be asked to wear earplugs or earphones while in the magnet.

b. Steps taken to minimize the risks.

Participants will be carefully screened over the phone prior to being scheduled, to assure that they meet study criteria. tDCS stimulation will be ramped up over the first 15 seconds of stimulation in order to eliminate the sensation of tingling that can occur under the electrodes during the initial moments of tDCS application. The participant may stop testing or the intervention any time. There will be emergency personnel and equipment on hand for your safety.

c. Plan for reporting unanticipated problems or study deviations.

Adverse events will be monitored during the entire visit by the study team. The families will be given telephone numbers of study team as well. The study physician (Dr. Argye Hillis) will be notified immediately if any adverse events are reported. Adverse events will be monitored until they are resolved or clearly determined to be due to a subject's stable or chronic condition or intercurrent illness. Medical care will be provided, as defined in the informed consent, for any adverse event related to trial participation. Appropriate medical care will include initiating transport to the Emergency Department of The Johns Hopkins Hospital for evaluation when necessary. All adverse events, regardless of intensity or causality, will are to be recorded in the study documentation and reported to the JHU IRB. Any serious adverse events will be reported to the JHU IRB within 24 hours.

Plan for dealing with incidental findings: All MRI scans will be read by Dr. Kraut who is willing to review our scans if there is anything new. If unexpected abnormalities - incidental findings - are seen (which is unlikely, as every patient will have had a clinical MRI as part of their evaluation for stroke), the patient will

be asked permission to contact the primary care physician about the abnormality, and will be offered a timely appointment with a neurologist (Argye E. Hillis, MD) if appropriate.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Participation in this study should not put participants in any legal risk, even in the case of a breach of confidentiality. We will undertake every effort to keep the information in the study confidential. Participants will be assigned a code number for the scans in order to keep the information confidential. The computers on which the information will be stored are password protected. Everybody involved in the study will have completed the appropriate HIPAA training and are fully aware of confidentiality issues. No names will be included in any publications resulting from this work.

e. Financial risks to the participants.

No financial risk is involved. Only participants who are interested in trying word retrieval therapy with tDCS and can be in Baltimore for the therapy as well as the follow-up sessions will participate in the study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

We cannot ensure that this research will provide any direct, sustainable benefit to the participants. It is possible that most participants will benefit from the present therapeutic intervention. Participants may or may not learn strategies to facilitate word retrieval and this knowledge may or may not generalize to other items or functions. Completion of this project will result in better understanding whether and how tDCS coupled with behavioral therapy may help individuals with post stroke aphasia.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will not be paid for participation in the treatment portion of the study. Participants will be paid $100 if they receive MRI scans pending funding. There is no penalty for not completing a tDCS session.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There is no cost to the participants for participating in the study.

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