C-STAR Project 2
Stimulating Language in Subacute StrokE (SLISSE)
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Protocol
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Johns Hopkins Medicine - eForm A

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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 transcranial direct current (tDCS) stimulation during language therapy for naming in individuals with aphasia in the acute and subacute post stroke period (i.e., within three months post stroke). Naming difficulties are a persistent and common symptom in aphasia after left-hemisphere (LH) stroke. Behavioral therapy (speech and language therapy; SALT) is the mainstay treatment for post stroke aphasia (Brady et al., 2012; Kurland et al., 2012). Therapy is beneficial for language recovery in stroke, especially in the first three months post stroke (Hillis, 2010; Lazar et al., 2010). 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. Anodal tDCS (A-tDCS) is most often applied to left hemisphere language areas to increase cortical excitability (reduce the threshold of activation). Most of studies are conducted in the chronic phase after stroke. Because neuroplasticity is greatest early after stroke, there is reason to believe tDCS might be most effective in the acute-subacute period. However, only two studies have evaluated tDCS paired with language therapy in group studies of acute to subacute aphasic stroke patients (Jung et al., 2011; You et al., 2011) and only one of these (You et al., 2011) was sham-controlled. Furthermore, no studies (of which we are aware) have combined A-tDCS with therapy to facilitate *naming* in post stroke aphasia, as shown to be effective in studies of chronic stroke (Baker et al., 2010).

In this project, we intend to investigate whether tDCS combined with SALT improves naming individuals with aphasia in the acute and subacute post stroke period, more than tDCS alone in a randomized, double-blind, sham-controlled trial. We hypothesize that A-tDCS over a targeted region and 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. We will compare the effect size in this study to the effect size obtained in the ongoing CATES trial (PI: Julius Fridriksson, University of S. Carolina), which uses the identical computer-delivered SALT + tDCS vs sham in chronic stroke, to evaluate the optimal timing of tDCS after stroke. We will explore whether or not the use of selective serotonin reuptake inhibitors (SSRIs) modifies the effect of tDCS on SALT in acute and subacute stroke,

and whether tDCS influences resting state connectivity in functional MRI (rsfcMRI) and/or functional Near-Infrared Spectroscopy (fNIRS).

We will also investigate the extent that the presence of genetic polymorphisms affect therapy outcomes. All participants will be asked to provide a saliva sample for the purpose of genotyping for BDNF (brain derived neurotrophic factor) and the FOXP2 gene (forkhead box p2). BDNF is a growth factor that has been shown to promote plasticity. Some individuals are carriers of the VAL66MET polymorphism, which leads to reduced BDNF secretion, and potentially decreased outcomes in aphasia therapy. Participants will be allowed to decline genetic testing. We will evaluate if there are any differences between participants who decline and those who agree to the testing.

The FOXP2 gene is the first gene that been implicated in speech-language impairment. Specifically, the FOXP2 polymorphism rs17137124. This gene has been implicated in neurogenesis and synaptogenesis, but little is known about its role in post-stroke recovery in humans. However, in a mouse model, FOXP2 expression has been related to the recovery of vocalization.

In order to investigate the extent that the presence of these polymorphisms affects therapy outcomes a DNA Genotek Oragene-DNA-OG500 kit will be used. Each kit contains a small tube that collect saliva. Participants will be asked to spit into the tube until 2 milliliters of saliva has been acquired. Participants will be provided with written/picture instructions (see attached Oragene DNA User Instruction). The process of delivering a saliva sample takes approximately 2-5 minutes. Sample tubes will be labeled with participant number and date of acquisition. For participants who have already completed the study, we will request that they either; i) come to the SCORE Lab to supply a sample, ii) allow us to meet them at their home to obtain a sample, or iii) for participants not living in the Baltimore areas, we will ask them to complete the sample by mail. If participants are to complete the sample by mail, they will be asked to complete and return the provided consent form with their sample. We will ask that they call one of the treating clinicians if they need help providing the sample, and a SLP will guide them through the instructions. We will provide all postage for participants to mail their sample to the lab. Also, we will use the SCORE Lab's address as the return address to ensure confidentiality.

All samples will be stored in DNA Genotek DNA storage boxes and locked in a storage cabinet in the lab. Samples are stable at room temperature for up to 5 years. All samples will be labelled with participant numbers.

2. Objectives

Primary Objective (intervention): To determine whether A-tDCS coupled with SALT will improve naming performance of participants with post stroke aphasia more efficiently and for greater duration than SALT 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 twice (and averaged to reduce variability) on two consecutive days immediately before treatment starts and twice after treatment is completed. The change will be computed as the difference in the number of correctly named items comparing the average of the two pre-treatment PNT assessments to the average of the two post-treatment PNT sessions. Naming errors will also be analyzed and categorized as semantic paraphasias, phonological paraphasias, mixed (semantic and phonological paraphasias, non-responses, unrelated responses.

The Primary Hypothesis 1a: A-tDCS over a targeted region coupled with computer-delivered SALT is associated with greater gains in accuracy in naming pictures, compared to sham coupled with the same computer-delivered SALT in post stroke aphasia. To test this hypothesis, we will compare the change in means of outcome measures in the group who received sham versus the group who received tDCS

(collapsing across localization subgroups). The primary outcome variable will be change in accuracy of naming untrained items within one week after treatment ends. The null hypothesis is H_0: $\mu_1 = \mu_2$, where μ_1 is the mean change in accuracy of naming untrained items between baseline and one week post-treatment in the A-tDCS group and μ_2 is the mean change in accuracy of naming untrained items between baseline and one week post-treatment in the sham group.

Primary Analyses: The primary analysis will compare change in accuracy of naming untrained items between groups (A-tDCS versus sham) in a two-sample *t*-test for the Intent-to-treat sample. For participants who do not complete the one week post-treatment assessment, the post-treatment value will be imputed using a multiple imputation approach assuming a monotone missing mechanism and missing is at random (MAR). As a sensitivity analysis, the primary outcome analysis will be repeated using all available follow-up data (without explicit imputation) in a mixed effects model of the change from baseline in naming accuracy adjusted for baseline (with Week 1, 5, or 20 as a categorical variable and a random effect for subject). Similar analyses will be done for the change in accuracy of trained items.

If we accept the null hypothesis, then tDCS is considered clearly ineffective (in improving anomia in stroke patients) and will not be considered for further study. If we reject the null hypothesis, we would consider undertaking a Phase III study of tDCS.

Power: We expect to enroll 50 Persons with Aphasia (APHASIC PARTICIPANTS) over four years, and expect 40-45 will complete the study. We predict no difficulty recruiting at least 10-15 APHASIC PARTICIPANTS each year after subacute stroke, as the PI has recruited an average of 53 APHASIC PARTICIPANTS due to acute left hemisphere ischemic stroke each year in her previous studies of aphasia recovery. If sample size in each group is 20, (a total sample size of 40), we will have 89% power to detect a difference in means of 23 (the difference between a A-tDCS mean change in accuracy, μ_1, of 33 and a sham mean change in accuracy, μ_2, of 10) assuming that the standard deviation of change for both groups is 22.2 using a two group *t*-test with a two-sided alpha of 0.05. These mean changes for tDCS and sham and standard deviation of change are based on the one published sham-controlled study of tDCS combined with SALT in subacute stroke (You et al, 2011).

Secondary Analyses: In secondary analyses, we will evaluate the effect of A-tDCS versus sham on change in lexical features of discourse, NIH Stroke Scale (NIHSS) (Lyden et al., 1999), modified Rankin Scale (mRS) (Banks et al., 2007; Rankin 1957), Stroke Impact Scale (Duncan et al., 1999) as well as Content Units (CU) and syllable/CU in the “Cookie Theft” picture description (Craig et al., 1993; Yorkston & Beukelman, 1980). Secondary analyses will also examine if any effects of A-tDCS vary across participants with different characteristics such as SSRI use, age, education, time of initiation of treatment, previous SALT, and lesion volume. To address this, a regression of change in naming accuracy, which includes main effects and interaction terms with treatment group for these characteristics will be used. This model will adjusted for treatment and time as described above for the mixed effects model. Given the small sample size and since this is a secondary analysis, a significance level of 0.10 will be used to retain main effects or interaction terms with treatment in the final reported model. Finally, within the tDCS treatment group, we will compare mean change in naming untrained pictures for the fMRI localization versus the structural localization subgroups (n=10-13 per subgroup). If there is a trend for the fMRI localization subgroup to show greater gains than the structural localization subgroup, we will include this comparison in a Phase III trial.

Secondary Objectives

Hypothesis 1b: The effect of A-tDCS will be greater in subacute stroke than reported in chronic stroke, the mean (95% CI) changes from baseline to 1 week, 5 weeks, and 20 weeks after the end of treatment will be reported for the subacute patients enrolled in this project and the chronic stroke patients enrolled in the Transcranial Direct Current Stimulation to Treat Aphasia: Phase II Trial (U01 DC011739; CATES Trial; PI: Julius Fridriksson) conducted at the University of South Caroline and the Medical University of South Carolina. The current trial is being conducted in collaboration with our colleagues at Medical University of South Carolina and University of South Carolina, including Dr. Fridriksson, who has designed and published previous studies using the computer-delivered SALT.

Hypothesis 2a: Within the first three months after stroke, improvement in naming untrained pictures is negatively influenced by increased time to initiate treatment; but this effect of time is mitigated by taking SSRIs continuously from stroke onset because SSRIs can increase the window for neuroplasticity. To test this hypothesis, we will compare model 1 with model 2. Model 1 will be a linear regression of change in naming accuracy from baseline to 1 week post-treatment with the following regressor/predictor variables: treatment group (A-tDCS or sham), age, education, time from stroke onset to initiation of treatment (in days). Model 2 will include the regressors from models 1 and an indicator of SSRI use since baseline (yes= if patient had used SSRIs continuously from stroke onset, no=otherwise). We predict that in model 1, time from stroke onset to initiation of treatment (in days) will be negatively associated with the response variable. In model 2, we predict that time from stroke onset will no longer be associated with outcome; after adjusting for SSRI use (and all else in the model), the type III test for the effect of time from stroke onset will not be statistically significant and the magnitude of the parameter estimate will change by more than 10%.

Hypothesis 2b: SSRI use since stroke onset is associated with greater gains with all treatments in the subacute period, independently of depression. To test this hypothesis, we will collapse aphasic participants across treatment groups, and compare the primary outcome measures for aphasic participants who have continuously taken SSRIs to aphasic participants who have not taken SSRIs. If SSRI use enhances plasticity at the subacute stage, it might augment the effect of A-tDCS and SALT without tDCS. Therefore, we predict that A-tDCS or sham combined with SALT over 15 sessions will be associated with greater gains in accuracy in naming untrained pictures in APHASIC PARTICIPANTS who have been taking SSRIs continuously since stroke onset, compared to the identical interventions in APHASIC PARTICIPANTS who have not been taking SSRIs. APHASIC PARTICIPANTS who have taken SSRIs for only part of the time will not be included in the analysis. Based on a recent survey of the inpatient stroke service, we predict about 50% of participants (n=20) will have taken SSRIs continuously, and almost 50% (n=17-20) will not have been exposed to SSRIs since stroke. The adjusted mean change (95% CI) in naming accuracy on untrained stimuli from baseline to 1 week, 5 weeks, and 20 weeks post-treatment for the SSRI-treated and the SSRI-untreated groups will be estimated using a mixed effects model adjusting for treatment group, baseline naming accuracy, time (with week 1, 5, or 20 as a categorical variable and a random effect for subject), and any subject characteristic found to be important in the secondary analysis (age, education, time of initiation of treatment, previous SALT and lesion volume, and interactions with treatment). We will then evaluate the independent effects of SSRI use, depression (measured at each time point with Patient Health Questionnaire-9, PHQ-9, Williams et al., 2005), and tDCS versus sham on the primary outcome variable using a multiple regression. Although we may not have the power to detect a significant effect of SSRIs, a few studies with similar small numbers have reported significant effects of SSRIs on stroke recovery measured with less sensitive measures such as the mRS. The goal of this exploratory aim is to determine whether or not we need to control for SSRI use in a subsequent clinical trial of A-tDCS in subacute stroke.

Hypothesis 3: A-tDCS over nonlesioned regions of interest (ROI) modifies functional connectivity, measured with rscfMRI, specifically between nodes of the "language network" and its homologues, relative to sham conditions. To test this hypothesis, we will carry out rsfcMRI before any treatment and after treatment (sham or tDCS). We will collapse data across participants with similar locations of lesions (e.g., left cortical+subcortical superior division MCA; or left thalamus only). For each lesion group, we will evaluate mean change in: (a) homologous connectivity (between left and right homologues); and (b) within network intrahemispheric connectivity, for each ROI within "language network": left posterior inferior frontal gyrus (PIFG), prefrontal cortex (PFC); posterior superior temporal gyrus (pSTG); anterior temporal lobe (ATL); posterior middle temporal gyrus (pMTG), posterior inferior temporal gyrus (pITG); and angular gyrus (AG). These areas were selected because they are frequently activated in naming and other semantic tasks, and so they would be plausibly activated by the treatment task. We will compare changes in connectivity from (1) clinical baseline to pre-treatment; (2) pre-treatment to post-treatment (A-tDCS or sham). We expect greater change after A-tDCS than sham. For each lesion group, we will also evaluate mean change in homologous connectivity and within network intra-hemispheric connectivity for each ROI within control areas: motor network (precentral gyrus and supplemental motor cortex), and "default network" (posterior cingulate, medial prefrontal, precuneus, amygdala, medial inferior parietal cortex). We expect changes in connectivity associated with tDCS to be greater in the language network than in other networks, measured with ANOVA. This hypothesis will be tested for participants who have rsfcMRI at all time points. We expect up to 20% (8 aphasic participants) will decline MRI or will be ineligible due to contraindication for MRI. A final number of 32 participants with longitudinal MRI should be adequate to test our hypothesis, based on previous studies of rsfcMRI that have shown significant changes in rsfcMRI in language network associated with recovery with smaller number of participants.

We will also examine functional connectivity with resting state fNIRS. The fNIRS protocol is expected to take up to 60 minutes and will be completed in the same location in which we administer behavioral assessments. fNIRS is a safe, non-invasive, and flexible modality for brain imaging. It capitalizes on the fact that near-infrared light can propagate several centimeters through tissue because of low optical absorption by hemoglobin and water at specific wavelengths. During an fNIRS experiment, an array of light sources and detectors affixed to a cap is placed on the scalp, and the measures from these different channels allow the reconstruction of an image of the hemodynamic response. fNIRS has emerged as a complementary technology to other brain imaging and monitoring modalities (e.g., EEG, fMRI). Previous research (Huppert et al., 2006; Strangman et al., 2002) in healthy populations has shown that the hemodynamic response captured in fNIRS is similar to that measured in fMRI. Collecting both fMRI and fNIRS data at each time point in the present study will allow us to compare these techniques in stroke. Unlike MR imaging, fNIRS has no contraindications (e.g., implanted ferrous material) and is portable. Thus, if a patient declines or is unable to complete research MRI scans, we will be able to offer fNIRS as an alternative option. Similar to rsfcMRI, "resting" fNIRS will allow us to determine intrinsic functional connectivity between regions of the brain at each stage of the study. At each time point, patients may also participate in task-related fNIRS sequences during which they will be asked to perform language tasks. The fNIRS data will complement the fMRI sequences and will allow us to determine how changes in brain activity patterns are related to treatment (A-tDCS or sham).

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 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. It is has not yet been demonstrated that its effects are specific to the targeted networks. We hope to show in this project that tDCS coupled with language therapy influences connectivity within the language network (regions activated during the naming task), but not connectivity within or across unrelated networks.

tDCS in Aphasia Research

The positive effects of tDCS in language functions are identified in studies of healthy controls, individuals with aphasia, and in individuals with neurodegenerative disorders, such as PPA. In healthy individuals, excitatory A-tDCS administered to left perisylvian brain areas can improve language processing (Flöel et al., 2008; Iyer et al., 2005; Sparing et al., 2008) when compared to sham stimulation. In addition, a handful of studies utilized fMRI to elucidate the neural underpinnings of language improvement due to anodal tDCS in healthy individuals (Holland et al., 2011; Meinzer et al., 2012; 2013; 2014). There is burgeoning literature of tDCS studies in aphasia. Studies vary in their design as well as the regions that are targeted for tDCS.

Most of studies are conducted in the chronic phase after stroke. Only two studies have evaluated tDCS paired language therapy in group studies of acute to sub-acute aphasic stroke patients (Jung et al., 2011; You et al., 2011) and only one of these (You et al., 2011) was sham-controlled. In the Jung et al. (2011) study, the individuals with milder degrees of aphasia made the greatest language improvements following ten days of therapy paired with tDCS. You and colleagues (You et al., 2011) evaluated 2mA tDCS over superior temporal gyrus (STG) paired with language therapy in 21 aphasic individuals, comparing three groups of seven patients each who received: cathodal right STG, anodal left STG, or sham tDCS. Greater gains in auditory comprehension were observed in patients who received cathodal tDCS (17%) compared to sham (10%) or anodal tDCS (10%). However, those who received cathodal tDCS were the least impaired on auditory comprehension at baseline, making it difficult to sort out the effects of tDCS. Furthermore, four of seven patients in the anodal tDCS group had lesions of the left STG, so it is not clear that they had structurally intact cortex beneath the left STG stimulating electrode, which may account for the negative results compared to sham. Thus, there is insufficient evidence to determine if tDCS augments SALT in facilitating aphasia recovery at the acute or sub-acute stage post stroke. However, these two studies show that in a fairly large number of patients (n=58) that 1-2mA tDCS is well tolerated and safe when delivered for 10 days in combination with language therapy.

No previous studies have directly evaluated the comparative effectiveness of tDCS on augmenting SALT at different time points relative to stroke onset. The timing of treatment may be an extremely important variable in both the duration and the mechanism of effects, as rodent studies and human studies indicate that there is a “sensitive period” during the first month or so after ischemic stroke during which there is increased responsiveness to motor training (Zeiler & Krakauer, 2015). During this time-limited sensitive period, the unique molecular, physiological, and structural milieu allows heightened plasticity through mechanisms that are qualitatively and quantitatively distinct from plasticity mechanisms that are observed in the absence of stroke or after chronic stroke (Krakauer et al, 2012; Zeiler & Krakauer, 2013; Ng et al., 2015). It is only during this period that increasing (Schabitz et al., 2004) or decreasing brain derived neurotrophic factor (BDNF) (Ploughman et al., 2009) e.g., through neuromodulatory therapies like tDCS,

has been shown to augment or prevent recovery. In humans, this period of plasticity for language recovery may last as long as three months (Lazar et al., 2010). Thus, it is plausible that tDCS would have its greatest effects in the first three months after stroke.

It is possible that this "sensitive period" for neuroplasticity might be extended or augmented pharmacologically. One randomized placebo-controlled clinical trial showed that the SSRI, fluoxetine, when administered early after stroke and continued for three months significantly enhanced motor recovery (Chollet et al., 2011). The positive effects were independent of effects on depression or mood. A recent meta-analysis indicated that patients treated with SSRIs after stroke were less likely to be dependent, disabled, and/or neurologically impaired (Mead et al., 2014). We also recently found that use of antidepressants (nearly always SSRIs) from stroke onset through six months or later was an independent predictor of aphasia recovery measured with the Western Aphasia Battery-Revised (Kertesz, 2007) after controlling for infarct volume, age, education, and time since onset (see preliminary studies). The mechanism underlying the effect of SSRIs on stroke recovery has not been proven, but it is plausible that it is related to the influence of SSRIs on synaptic plasticity. For instance, it has been shown that fluoxetine can restore time-dependent cortical plasticity in visual cortex of adult rodents (Vetencourt et al., 2008). Furthermore, Ng et al. (2015) and Zeiler et al. (2013) demonstrated in a mouse model of focal stroke that responsiveness to training reach-to-grasp was diminished when training was delayed, compared to when it was initiated 24 hours after stroke. However, if fluoxetine was provided to the mice early after stroke, then maximal response to training was observed in the delayed training condition (indicating that the SSRI extended the sensitive period for training, presumably via neuroplasticity).

No previous studies have evaluated the influence of SSRIs on effectiveness of tDCS. Surprisingly few studies have evaluated any factors that account for individual differences in responsiveness to tDCS, other than site of lesion. In one study of chronic stroke (Marangolo et al., 2014) there were no differences between sham and tDCS groups in BDNF serum levels after tDCS stimulation, but there was a positive correlation between percent change in BDNF level and improvement in naming accuracy in the tDCS condition only. Thus, a subset of individuals may show a change in BDNF in response to tDCS (and improvement in naming accuracy) even in chronic stroke. We can conjecture these might be individuals taking SSRIs or those with otherwise extended sensitive periods.

Animal models of stroke have provided extensive evidence for the effectiveness of pharmacological modulation of recovery after ischemic stroke. Most studies have evaluated motor recovery after infarcts made in motor cortex. After small cortical infarcts, a variety of activity-dependent mechanisms facilitate reorganization of cortical function (Hermann & Chopp, 2012; Murphy & Corbett, 2009) including dendritic spine elaboration (Brown & Murphy, 2008; Ueno et al., 2012), axonal sprouting (Dancause et al., 2005) and change in strength of pre-existing synapses (DiFilippo et al., 2008; Jaenisch et al., 2010; Yao et al., 2005). Animal studies indicate that synaptic plasticity can be best augmented by manipulating several neuromodulators simultaneously (Bao et al., 2001; Kilgard & Mersenich, 1998; Schultz, 2002) providing a theoretical basis for combining behavioral therapy, pharmacotherapy, and tDCS. However, no previous studies have evaluated the combination of any pharmacotherapy and tDCS for aphasia. In fact, few studies have adequately evaluated the effect of pharmacotherapies on augmenting aphasia rehabilitation (Llano & Small, 2015) The few randomized, controlled trials have evaluated: dextroamphetamine (Walker-Batson et al., 2001), dopamine enhancement (Ashtary et al., 2006; Seniów et al., 2009), piracetam (Huber et al., 1997), donepezil (Berthier et al., 2003), or memantine (Berthier et al., 2009). Augmentation of SALT with SSRIs to improve aphasia has not been adequately evaluated (de Boissezon et al., 2007).

It is plausible that SSRIs, which elevate synaptic serotonin, might enhance recovery by augmenting synaptic plasticity. Seratonin influences cortical reorganization (Gu & Singer, 1995; Jitsuki et al., 2011; Vetencourt et al., 2011) and adult neurogenesis in the hippocampus (Daszuta, 2011; Li et al., 2009) and may increase BDNF (Martinowich & Lu, 2007) (which may be a critical modulator of recovery implicated in the mechanism of tDCS as well. These mechanisms may account the positive effect of SSRIs (fluoxetine) on post-stroke motor recovery in humans (Chollet et al, 2011). In the cognitive domain, Jorge et al. (2010) reported that another SSRI (escitalopram) given in subacute stroke improved performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), again independently of the effect on depression. Although there have been no randomized clinical trials, several small studies have shown positive effects of antidepressants on language outcomes (Kimura et al., 2000; Narushima et al., 2000; Tanaka, 2007) (but see Laska et al., 2005). Furthermore, there is high rate of post-stroke depression, ranging from 30 – 60% (Barker-Collo, 2007; Robinson et al., 1984) and post-stroke depression can be significantly reduced with pharmacotherapy (Hackett et al., 2008) Thus, there may be several positive effects of SSRIs after stroke; but the effects on mood and recovery appear to be independent (Chollet et al., 2011). We hypothesize that delay in initiation of A-tDCS/sham combined with SALT (within the first three months) will negatively impact the primary outcome measure (improvement in naming untrained stimuli post treatment), except in aphasic participants using SSRIs from stroke onset through post-treatment (Ng et al., 2015). However, SSRIs may enhance neuroplasticity, and augment effects of A-tDCS and/or effects of both SALT and A-tDCS in subacute stroke.

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

After informed consent is received, a neurological examination will be performed and multiple screening assessments will be conducted including a tDCS and MRI safety screening (see below). If the participant passes the initial screening portion, speech and language diagnostic testing will be conducted during the same visit (Visit 1). During the next visit (Visit 2), participants will undergo a second baseline assessment of naming ability and assessment of connected speech. On that visit, participants who have no contraindication for MRI will be randomized to (1) fMRI electrode placement or (2) structural electrode placement. All participants who have no contraindication will have structural and rsfcMRI. Those randomized to fMRI electrode placement will also participate in the naming paradigm during the MRI. Participants may also undergo fNIRS at this visit. The third visit will include electrode positioning and tDCS treatment administration. Participants will receive 15 sessions (Visits 3-17) of tDCS + SALT administration. At the beginning of Visit 3, eligible participants will be randomized to receive either A-tDCS (1 mA) or sham-tDCS (placebo) for 15 sessions (20-minutes per each 45-minute behavioral treatment session) over the course of three weeks. 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. To assess cardiovascular arousal, blood pressure and heart rate will be measured before and after each session. Additionally, discomfort ratings will be recorded following the end of each session using the Wong-Baker FACES Pain Rating Scale (Wong & Baker, 1988) and a weekly neurological exam will be administered by a neurologist.

Neither the participant nor the clinician monitoring and setting up the treatment will have knowledge of the treatment condition (A-tDCS versus sham).

Utilizing a computerized picture naming assessment (PNT), all participants will be assessed at several different time points throughout the experiment: twice immediately before and twice the week immediately following the fifteenth and final treatment session; twice at five weeks follow-up after the end of treatment; and twice at 20 weeks after the end of treatment.

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 rsfcMRI at Visit 2, following the 15th treatment session (Week 1 after the end of treatment), and at 5 weeks after the end of treatment. Participants who agree to participate in the fNIRS portion of the study will have fNIRS at Visit 2, following the 15th treatment session (Week 1 after the end of treatment), at 5 weeks after the end of treatment, and at 20 weeks after the end of treatment.

Additionally, we will collect saliva samples for the purpose of genotyping.

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. Review inclusion/exclusion criteria.
3. Obtain medical history.
4. Conduct neurological examination.
5. Administer the A-tDCS safety screening.
6. Administer the MRI safety screening.

Procedures for Diagnostic Testing (Visit 1)
If the participant passes the screening portion, diagnostic testing will be conducted during the same visit. The following diagnostic testing procedures will be performed:

1. Administer the Western Aphasia Battery-Revised (WAB-R): The WAB-R will characterize the participants' overall language impairment through the evaluation of the main clinical aspects of language functioning, including speech content, speech fluency, auditory comprehension, repetition, and naming. The WAB-R allows for the differentiation of these specific language abilities, as well as the classification of aphasia type. The WAB-R also yields a composite score, the Aphasia Quotient, which provides an overall measure of severity, in which lower scores denote more severe aphasia (Kertesz, 2007). Both the AQ and aphasia type will be used to stratify participants for randomization. This randomization will be done using the Web Data Collection Unit (WebDCU™), developed at Medical University of South Carolina, after data for the participant are entered by the speech-language pathologists). Speech-language pathologists (SLPs) will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 30-45 minutes.

For this project, the WebDCU™ workscope will include development and maintenance of their web-based clinical data management system, behavioral data storage, and providing ad hoc statistical expertise. The requirements for individual protocols can be highly variable due to differences in study design as well as the specific needs of investigators, sponsors, and project and data management teams. The generic structure of WebDCU™ is flexible enough to meet the unique needs of each specific protocol. The WebDCU™ uses a relational database structure for Case Report Form (CRF) data, operational data and study design components, such as subject randomization, subject visit and treatment schedule, data collection schedule, and subject study progress. Study phase/visit transfer logic is directly implemented during the system installation, which provides a solid foundation for study protocol compliance and helps to minimize operational errors caused by missing information or human mistakes. WebDCU™ identifies and tracks each patient based on a unique identifier. Once a patient's baseline information has been reported in WebDCU™, all subsequent testing and treatment data are entered online using customized CRFs that are specifically designed with the specific needs of this project in mind. The DCU will develop and validate the web-based data collection system that will house the study databases. This will include programmed data rule checks (i.e., logic checks) for the specified outcomes/data points, based on the final versions of the CRFs. The web-based system will include subject enrollment and treatment randomization, data entry screens for each study CRF (based on the data collection schedule), data validation, data audit trail, and a data transfer mechanism. All patient data are entered by speech-language pathologists who conduct the scheduled behavioral testing and treatment sessions. In addition, specific CRFs will be developed to track the completion of specific MRI scans and for site monitoring.

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): The PPTT is a test of semantic processing. This test assesses the degree to which a participant can access meaning from pictures and words. 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, or a difficulty in retrieving semantic information from words, or, in the case of a naming failure, a difficulty in retrieving the appropriate spoken form of the word (Howard & Patterson, 1992). SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-20 minutes.

5. Administer naming screen used to verify that participants comprehend task requirements: Refer to computer setup for the treatment for this practice screen.

6. Administer the NIH Stroke Scale (NIHSS) (Lyden et al, 1999): Clinicians will be certified in administration of the NIHSS by taking a web-based course offered by the American Heart Association. The NIHSS will provide a measure of overall stroke severity. The SLP will also record the description of the "Cookie Theft" picture on the NIHSS, which will also be analyzed for Content Units (CU) and Syllable/CU (Craig et al., 1993; Yorkston & Beukelman, 1980). This test will be repeated at Week 5 and Week 20 after the end of treatment.

7. Administer the Stroke Impact Scale (SIS) (Duncan et al., 1999).

Procedures for the Computerized Naming Assessments (Visits 1, 2 & all follow up evaluations)
The following procedures will be performed during Visits 1, 2, and each follow-up evaluation:
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 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 10-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.
4. Start internal web-camera for audio-visual recording. Administer the Naming 80 Assessment (naming of 80 items from the training set) 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 10-seconds have elapsed.

Procedures for the "Cinderella Story" Picture Discourse Analysis and Depression Scale (Visit 2, 18, 20, and corresponding baseline and follow-up evaluations for each treatment period)
The following procedures will be performed during Visits 2 (baseline), 18 (immediately after), 20 (5 week follow-up), and corresponding baseline and follow-up times for each treatment period, as well as 6 months after both the acute phase and the subacute phase.

1. The "Cinderella Story" is to be completed following the administration of the naming assessments, 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.
5. Administer the PHQ-9. This 9 item scale has high sensitivity and specificity for depression, compared to structured psychiatric interview, in individuals with stroke.

Procedure for Randomizing to fMRI Electrode Placement vs Structural Electrode Placement (Visit 2)
The SLP will take the next sequential sealed envelope (numbered from 1 to 50) from a box, and open it. The card will state "fMRI" or "structural." 25 of the cards will state "fMRI" and 25 will state "structural."

Procedures for Structural and Resting State Functional Connectivity fMRI Examination (Visits 2, 18, 36) (all participants who consent to MRI and have no contraindication)

The following procedures will be performed:

1. Run the participant on a 10-minute rsfcMRI exam during visits two and immediately after treatment periods 1 and 2: Instruct the participant to lie still in the scanner, eyes open.
2. Run the participant on high-resolution anatomical MRI scans during each of the same visits Instruct the participant to do lie still during these scans.

Procedures for functional Near-Infrared Spectroscopy (fNIRS) Examination (Visits 2 and follow-up evaluations) (all participants who consent to fNIRS)
The following procedures will be performed:

1. Run the participant on a 10-minute resting fNIRS exam during visits two and at follow-up evaluations: Instruct the participant to sit still, eyes open.
2. Run the participant on task-based fNIRS scans during each of the same visits
Instruct the participant to do sit still and complete the tasks as instructed to the best of their ability.

Procedures for Naming Paradigm (for participants who are randomized to fMRI electrode placement) (Visit 2)
The following procedures will be performed:
1. Run the patient on a 10-minute fMRI exam during visit two: Instruct the patient to overtly name pictures representing nouns (n = 40) once they appear on the screen and to say nothing when checkerboards appear on the screen (n=40). The pictures will be presented for 2 s each on a back-projected mirror located on top of the head coil. A non-ferrous microphone will be placed 1-3 cm from the patient's mouth and used to record naming attempts, which will be recorded with sufficient clarity for off-line scoring by a trained speech-language pathologist.

Procedures for Electrode Positioning (Visit 3)
The following procedures will be performed:
1. Fit the patient with a latex scalp cap and instruct them to sit as still as possible during this process.
2. Identify and label the following six anatomical landmarks on the patient's scalp cap utilizing a permanent marker: 1) left ear; 2) right ear; 3) left eyebrow; 4) right eyebrow; 5) head apex; and 6) occipital bun.
3. Upload the patient's anatomical T1 MRI scan (acquired from Visit 2) onto a computer utilizing MRIcro, a computer program that allows for the viewing of MRI images (www.mricro.com).
4. Employing MRIcro, select an anatomical location on the patient's T1 MRI scan (e.g., bridge of nose) by mouse-click.
5. Move the magnet sensor from the Flock of Birds magnetic tracking system to the location on the patient's head which mirrors the anatomical position selected in MRIcro from Step 4 and enter into the MRIreg software, a computer program that registers a high-resolution MRI scan of the head with scalp locations (www.mricro.com/mrireg.html).
6. Repeat Steps 4 and 5 until the following five anatomical landmarks have been entered into MRIreg: 1) left ear; 2) right ear; 3) bridge of nose; 4) head apex; and 5) occipital bun.
7. Press the 'correlation line' button of MRIreg after the five anatomical landmarks from Step 6 have been located.
8. Enter the coordinates of the area of the left hemisphere with either (1) the highest level of activation within the peri-lesional area during correct naming on the fMRI naming task in the 'desired MRI' boxes (these coordinates will be identified by Dr. Sebastian and forwarded to the SLP on patient-by-

patient basis) for participants randomized to the fMRI electrode placement, or (2) undamaged cortex to target in left inferior frontal gyrus (IFG), or if IFG is infarcted, undamaged cortex in left superior temporal gyrus (STG) to target, or if both left IFG and STG are infarcted, undamaged cortex in left prefrontal cortex (these coordinates will be identified by Dr. Hillis and forwarded to the SLP on patient-by-patient basis) for participants randomized to the structural electrode placement).
9. MRIreg will estimate the current distance of the magnet sensor wand from this point. Move the wand around the patient's head and once the most precise area is located, label the location on the patient's scalp cap with a star utilizing a permanent marker.

Procedures for Treatment
The following procedures will be performed:
1. Measure and record the participant's blood pressure and heart rate.
2. Carefully fit participants with their scalp cap (labeled from Visit 3).
3. Soak the 2 sponge electrodes in saline solution and place inside rubber electrode holders.
4. Place the anode electrode under the designated area on the scalp cap that was located during the electrode positioning process (marked with a star during Visit 4). Remove the cap and secure electrode placement with a self-adhesive bandage.
5. Place the reference cathode electrode on the participant's right orbito-frontal scalp (above the right eyebrow) and secure electrode placement with a self-adhesive bandage.
6. Connect the electrode cables to the relay box positioned between the tDCS stimulator and the lap-top computer used to maintain experimenter and participant blinding. Start the software used for blinding (see an icon "tDCS+aphasia" on the desktop) and enter the participant number (obtained on the DCU web site) in the designated place. Make sure that the screen of the "blinding" lap-top is placed out of participants' sight.
7. Turn on tDCS stimulator.
8. 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.
9. 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 male 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.
10. "Click" on the START icon on the "blinding" computer to simultaneously start stimulation and the computer treatment task.
11. Measure and record the participant's blood pressure and heart rate following treatment completion.

12. Record any Adverse Events experienced during the treatment session or since the last visit on the AE log.
13. Assess and record the participant's comfort rating using the Wong-Baker FACES Pain Rating Scale following treatment completion.

Procedures for Neurological Examination (Visits 8, 13, 18)
The following procedures will be performed:
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 the neurological examination administered during Visit 1 will be re-administered weekly by Dr. Hillis during the treatment phase.

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

After informed consent is received, a neurological examination will be performed and multiple screening assessments will be conducted including a tDCS and MRI safety screening (see below). If the participant passes the initial screening portion, speech and language diagnostic testing will be conducted during the same visit (Visit 1). During the next visit (Visit 2), participants will undergo a second baseline assessment of naming ability and assessment of connected speech. On that visit, participants who have no contraindication for MRI will be randomized to (1) fMRI electrode placement or (2) structural electrode placement. All participants who have no contraindication will have structural and rsfcMRI. Those randomized to fMRI electrode placement will also participate in the naming paradigm. Those who agree will also undergo fNIRS. The third visit will include electrode positioning and tDCS treatment administration. Participants will receive 15 sessions (Visits 3-17) of tDCS treatment administration. At the beginning of Visit 3, eligible participants will be randomized to receive either A-tDCS (1 mA) or sham-tDCS (placebo) for 15 sessions (20-minutes per each 45-minute behavioral treatment session) over the course of three weeks. 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.

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, the site investigators, and the clinical staff involved in this study will not know the treatment assignment. Select members of the statistical and Data Management Center will be partially blinded, i.e., they will know the treatment group assignment as A or B, but not whether the patient receives active tDCS or sham. The study statistician and the DSMB will have a sealed envelope with the treatment group identifiers. This envelope would only be opened if the study statistician is directed to open it by the DSMB or at the end of the futility study.

The randomization will take place centrally via the Trial Website. Subjects will be randomized 1:1 (A-tDCS: S-tDCS), controlling for clinical center, aphasia type, and severity (classified using the Western Aphasia Battery revised: WAB-R). The computer program developed at the DCU makes the treatment assignment based on the current status of treatment group distribution within each stratum as well as overall balance of treatment assignment. The randomization scheme will never be deterministic. The detailed randomization scheme and source codes will be provided in the Randomization Plan document.

A “Real-Time” randomization procedure is implemented via the Trial Website on the WebDCU™

System where the clinical center staff enters the basic baseline (e.g. aphasia type, and AQ severity) and eligibility information of a subject prior to enrollment. If the subject's eligibility status is confirmed, the computer program on the WebDCU™ server will evaluate the treatment arm distribution and generate a patient number based on the randomization scheme. The SLP enrolling the patient will not see the treatment assignment, only a numeric patient number which is entered into a software package that controls whether the tDCS given is A-tDCS or Sham. In order to mask treatment type (A-tDCS vs. Sham) for both patients as well as the SLPs administering the treatment session (i.e., setting up the tDCS and starting and monitoring the computerized treatment task), we use in-house software/hardware. As previously discussed, this setup allows for switching the tDCS on and off without any involvement from the patient or experimenter. The software is run on a lap-top computer connected to the tDCS stimulator. Treatment type is encoded in the software so that the administrator only needs to enter a patient and session number to start stimulation without knowing whether those specific numbers are associated with A-tDCS or Sham. The unblinded list of randomization codes and treatment assignments will be generated by the DCU and will be uploaded into the software by a software administrator who is not otherwise involved in the study.

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

Both groups will receive SALT, which is the current clinical standard of care for post-stroke aphasia. It is currently unknown whether or not tDCS augments the effect of SALT in the subacute phase after stroke. Therefore, a sham group is justified.

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.

<u>Changes to Procedures in the Event of a Pandemic</u>
Upon resumption of our clinical research investigating the use of transcranial direct current stimulation (tDCS) in subacute stroke in the wake of the COVID-19 emergency, 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.

- For face-to-face visits, we will primarily use the STAR Car, a mobile lab space (wheelchair accessible van) that would allow for isolated testing in lieu of testing in participants' homes or in our

testing rooms located at the hospital, thus minimizing the risk of possible exposure to COVID-19. If the STAR Car cannot be used for a particular session, we will perform 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.

- We will consent participants remotely. We will be using DocuSign, the Institution's approved and 21 CFR Part 11-compliant software, to obtain a secure electronic signature. Once the IRB approves our consent form(s), we will use the IRB-approved consent form(s) as the base for the DocuSign template. The IRB-approved document will not be altered other than to overlay locations where signatures, initials, dates or other DocuSign fields will be added to create the study-specific DocuSign template. We will send the consent to the participant via DocuSign, providing a participant-specific code in advance of sending the document via DocuSign, that will be required when the participant accesses and signs the consent. The consent discussion may take place via phone or video conference (e.g. Zoom). Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. When ready to sign, the participant will enter their code, verifying that the person signing the consent is the person that we spoke with previously, and sign the consent within the DocuSign system. (Note: For studies requiring multiple signatures, e.g. two parental signatures or if a witness is required, all individuals will receive codes in order to sign). Once the participant has electronically signed, the study team member obtaining informed consent will be notified that the electronic form is ready for his or her signature. Once signing is completed by all parties, both the study team and the participant can download the signed consent as a PDF. The study team will also have access to the audit log and the Certificate of Completion. The study team will load the signed consent into Epic. In instances where Docusign cannot be executed or the potential participant declines to use it, Teleconsent will still be used as opposed to in person consenting where possible to reduce unnecessary in person encounters specifically for a consent procedure. Participants will be provided with a copy of the Informed Consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in person visit. As a Physician/Mid-level provider consent signature is not required, the consent designee may proceed with teleconsent without an expectation for a follow-up in person consenting process. The consent designee must verify the participant physically signed the consent document either by viewing via video conference, obtaining a photo of the signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant or LAR will sign and date/time the informed consent document. The document is then mailed, emailed or faxed to the consent designee. The participant will be asked to return the original signed document on their first in person visit. If the Informed Consent form is mailed to the consent designee by the participant the IRB-approved consent designee will sign the copy, which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document. In all other instances, once received, the IRB-approved consent designee signs, dates/times the informed consent document. After the Informed Consent process is completed, the IRB approved study team member files the consent document in EPIC, including a note confirming the consent process. The entire consent document is also then filed in the research record.
- We have adapted testing so that tasks can be administered remotely via video conferencing. We will no longer see participants in the hospital for assessments. We will give patients the option of face-to-face visits in the STAR Car or remote assessment prior to treatment and at one, five, and twenty weeks post-treatment. Each enrolled participant who opts for remote assessment will be delivered a "tele-assessment kit" to complete assessments. These kits will include:

  - A laptop computer pre-loaded with the treatment apps, zoom for online videoconferencing with the research team and Team Viewer which will allow the research team to see the participant's computer to help with initial set-up and troubleshooting.
  - A high quality headset with a microphone to maximize communication with the research team online.
  - A mouse for optional use.
  - A mobile WiFi hotspot if a participant does not have an adequate WiFi connection at home.
- Our treatment protocol must be administered in person as the tDCS equipment is placed on the participant's head during each session. We will conduct treatment sessions in the STAR Car (or outside of the person's home, e.g. on a porch, if they prefer).
- 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. The entire STAR Car will be disinfected before 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 mask and gloves during face-to-face 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 face-to-face 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.
- We will discontinue research magnetic resonance imaging (MRI) scanning until deemed safe to resume by the appropriate Johns Hopkins policies/administration. Discontinuing research MRI scans will eliminate the need for participants to travel to the hospital for assessment sessions.
- We will still be able to collect some brain functioning measures with the use of functional near-infrared spectroscopy (fNIRS), which is already IRB-approved in our protocol. fNIRS uses light emitted from optodes in a cap worn by participants to measure brain activity. fNIRS setup and testing is mobile, allowing us to obtain brain activity measures in the STAR Car or participants' homes. fNIRS equipment will be disinfected prior to and following each session.

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 an acute ischemic 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 within 3 months of onset of stroke.
7. Participants must have an aphasia diagnosis as confirmed by the Western Aphasia Battery-Revised.

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

1. Previous neurological or psychiatric disease, including previous symptomatic stroke.
2. Seizures during the previous 12 months.
3. Uncorrected visual loss or hearing loss by self-report.
4. Use of medications that lower the seizure threshold (e.g., methylphenidate, amphetamine salts).
5. Use of NMDA antagonists (e.g., memantine).

6. History of brain surgery or any metal in the head.
7. 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 (Chattanooga Ionto 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 twice (and averaged to reduce variability) on two consecutive days immediately before treatment starts and twice after treatment is completed. The change will be computed as the difference in the number of correctly named items comparing the average of the two pretreatment. PNT

assessments to the average of the two post-treatment PNT sessions.

b. Secondary outcome variables

In addition to the primary outcome, several 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. We will also evaluate differences between treatment groups in QOL as measured by the Stroke Impact Scale, mRS, Content Units (CU) and syllables/CU in describing the Cookie Theft picture on the NIH Stroke Scale. 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.

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

Statistical Analysis

The primary hypothesis is that A-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. To test this hypothesis, we will compare the change in means of outcome measures in the group who received sham versus the group who received tDCS (collapsing across localization subgroups). The primary outcome variable will be change in accuracy of naming untrained items within one week after treatment ends. The null hypothesis is H_0: $\mu_1=\mu_2$, where μ_1 is the mean change in accuracy of naming untrained items between baseline and one week post-treatment in the A-tDCS group and μ_2 is the mean change in accuracy of naming untrained items between baseline and one week post-treatment in the sham group.

The primary analysis will compare change in accuracy of naming untrained items between groups (A-tDCS versus sham) in a two-sample *t*-test for the Intent-to-treat sample. For participants who do not complete the Week 1 post-treatment assessment, the post-treatment value will be imputed using a multiple imputation approach assuming a monotone missing mechanism and missing is at random (MAR). As a sensitivity analysis, the primary outcome analysis will be repeated using all available follow-up data (without explicit imputation) in a mixed effects model of the change from baseline in naming accuracy adjusted for baseline (with Week 1, 5, or 20 as a categorical variable and a random effect for subject). Similar analyses will be done for the change in accuracy of trained items.

If we accept the null hypothesis, then tDCS is considered clearly ineffective (in improving anomia in stroke patients) and will not be considered for further study. If we reject the null hypothesis, we would consider undertaking a Phase III studyof tDCS.

Sample Size Determination

We expect to enroll 50 participants over 4 years, and expect 40-45 will complete the study. We predict no difficulty recruiting at least 10-15 participants with aphasia each year after subacute stroke, as the PI has

recruited an average of 53 aphasic patients due to acute left hemisphere ischemic stroke each year in her previous studies of aphasia recovery. If sample size in each group is 20, (a total sample size of 40), we will have 89% power to detect a difference in means of 23 (the difference between a A-tDCS mean change in accuracy, μ_1, of 33 and a sham mean change in accuracy, μ_2, of 10) assuming that the standard deviation of change for both groups is 22.2 using a two group *t*-test with a two-sided alpha of 0.05. These mean changes for tDCS and sham and standard deviation of change are based on the one published sham-controlled study of tDCS combined with SALT in subacute stroke.

Multiplicity

Since this is a Phase I/II study, the false positive error rate has been relaxed (Schoenfeld, 1980). For a futility design the type I and type II error rates are reversed as compared to a traditional, superiority hypothesis. For the primary analysis, the probability of incorrectly declaring a drug futile is 0.1 (or 10%, type I error is the false negative rate). Given that the active tDCS comes from a distribution with a mean change of the control group (e.g. the treatment is the same as the sham), the probability of incorrectly moving to a Phase III trial is 0.15 (or 15%, type II error is the false positive rate).

For secondary outcomes and safety analyses, no adjustment of Type I error probability will be considered, since they will be treated as exploratory.

Missing Data

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the primary outcome measure, can be problematic. For the primary futility analysis we will impute missing data using multiple imputation (Rubin, 1987) assuming a monotone missing mechanism and missing is at random (MAR). Similar methods will be employed for secondary analyses and secondary outcomes. For safety data (e.g. AEs) no data imputation will be done.

Interim Analysis

No formal interim analyses are planned.

Adjusting for Covariates

The primary analysis will be adjusted for aphasia type, and baseline aphasia severity (AQ), education, time from stroke onset to time of treatment initiation, and number of previous SLP treatment sessions (prior to our study).

Secondary Analyses

In addition to the primary outcome, several 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. We will also evaluate differences between treatment groups in QOL as measured by the Stroke Impact Scale, mRS, Content Units (CU) and syllables/CU in describing the Cookie Theft picture on the NIH Stroke Scale.

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.

Post-Testing Phase
The longer follow-up post-testing phase will provide exploratory information on whether the immediate post-testing improvement after three weeks of treatment can be sustained. The mean (95% CI) changes from baseline to immediate (within one week) post-testing, five weeks (after the end of treatment) post-testing and 20 weeks (after the end of treatment) post-testing will be reported. Box and whisker plots will be produced to show the distribution of naming accuracy over time by treatment group. To explore the longitudinal data, a general linear mixed model (GLMM) will be constructed by tDCS group for the dependent variable (anomia). The GLMM will incorporate random subject effects to account for repeated measurements being made on subjects; the model will include time, aphasia type, severity, and clinical center as independent variables. A similar modeling approach may be applied to other secondary outcomes.

Safety Analyses
All adverse experiences will be summarized in terms of frequency, severity and relatedness to the study treatment using the MedDRA code. All subjects who received tDCS will be included in the safety analysis. At the end of the study, the cumulative incidences of adverse events are compared between the two treatment groups using Fisher's exact test at the two-sided alpha level of 0.05.

The repeated measures of the FACES pain rating scale will be compared by treatment group by fitting a repeated measures proportional odds model.

DSMB Reporting
The study biostatistician will generate closed and open DSMB reports semi-annually or more frequently, as determined by the DSMB. Each DSMB report provides cumulative summary statistics on enrollment; subject status in the study (e.g., number completed study, drop outs, etc.); baseline characteristics; safety data, including AEs and SAEs; and data quality information. The statistics for the closed DSMB Reports are provided by treatment group displayed as A or B. The open report contains aggregated statistics only, i.e., not by treatment group.

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

The present study involves that participants undergo MRI scanning. 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.

fNIRS

Near-infrared spectroscopy (NIRS) is a relatively new investigational tool. Although no adverse effects have been reported, it is possible that effects not yet reported may occur. The LED light in the NIRS devices used to make the measurements has low power (within the ANSI limit for long-term exposure to infrared light). Thus far, no hazard to patient, staff or third party has been observed. NIRS monitoring requires coupling “optodes” (optical sensors) to the skin on the scalp. This is achieved by fastening the optodes to a cap, placing the cap over the head and holding it in place with a strap placed under the chin or behind the head. The subject's hair may need to be parted in the location of the optodes to provide better coupling to the skin. The procedure does not cause pain or distress. Subjects will be asked to keep their head relatively still for several periods of up to approximately 10-15 minutes each while performing the tasks. However, the NIRS device will be made as insensitive as possible to head motion, and hence strict subject compliance is not essential. Fatigue and/or boredom from performing the tasks are the most likely risks in this study.

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) and the DSMB will be notified immediately if any adverse events are reported. The DSMB will determine if the adverse event is a serious adverse event. 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 and DSMB. Any serious adverse events will be reported to the JHU IRB and the DSMB 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. Please note that ALL of our patients, who will be recruited from Dr. Hillis' database, have MRIs at different times post-stroke. 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, primary investigator) 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 to participate in the study. There is no penalty for not completing a tDCS session. Participants will be reimbursed $40 for travel and parking for each therapy session and evaluation session if they provide their own transportation. The study will provide sedan service (through Freedom Car sedan service) for patients who do not have transportation.

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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