High-Definition Transcranial Direct Current Stimulation (HD-tDCS) in logopenic variant Primary Progressive Aphasia (lvPPA): Effects on Language and Neural Mechanisms.

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PROTOCOL SUMMARY

Title	**High-Definition Transcranial Direct Current Stimulation (HD-tDCS) in logopenic variant Primary Progressive Aphasia (lvPPA): Effects on Language and Neural Mechanisms.**
Principal Investigator	Elias Granadillo, MD
Study Site	Medical College of Wisconsin
Device Trial Phase	**Pilot Study**
Study Disease	logopenic variant Primary Progressive Aphasia (lvPPA)
Main Eligibility Criteria	• Clinical lvPPA or imaging-supported lvPPA • Age 45 years and older • Structural brain MRI done within the 3 years prior to enrollment.
Study Rationale	The logopenic variant of Primary Progressive Aphasia (lvPPA) is a neurodegenerative disorder often referred to as the 'language form' of Alzheimer's Disease (AD). The current conceptual disease framework assumes a relatively widespread neurodegeneration which causes patients to continue to use pre-existing, specific neural areas with declining efficiency. tDCS is a non-invasive, painless brain stimulation technique that appears to enhance language production when delivered during language training. To date, studies utilizing tDCS in lvPPA patients have been limited to conventional montages that are not suitable for focal targeting of brain tissue. High-Definition tDCS (HD-tDCS) is a recently developed system that allows for more focal stimulation based on increased current focality and intensity, and the individualized modelling of the patient's brain tissue. Considering this, use of HD-tDCS to target the most consistent neural correlate of lvPPA (the left posterior temporo-parietal cortex) should be explored.
Primary Objectives	Determine the efficacy of HD-tDCS for the improvement of language performance in lvPPA.
Secondary Objectives	(ii) evaluate the effects of HD-tDCS on functional connectivity using functional Magnetic Resonance Imaging (fMRI), and (iii) elucidate its effects on spontaneous neuronal oscillatory patterns using Magnetoencephalography (MEG).
Endpoints	• Primary outcome measurements: Language performance changes as assessed at baseline and after tDCS stimulation procedures (time frame: 2 weeks). • Secondary outcome measurements: (ii) Changes in brain functional connectivity as assessed at baseline and after tDCS stimulation (time frame: 2 weeks) (iii) Changes in abnormal patterns of neuronal frequencies and synchronizations as assessed at baseline and after tDCS stimulation procedures (time frame: 2 weeks).

Study Design	This clinical utility study is a randomized, double-blind, sham-controlled trial in which stimulation or sham will be administered to 20 subjects over the age of 45 years, with the order of treatments counterbalanced in a within-subject crossover design. Stimulation and sham sessions last 20 minutes and occur for 10 days over a 2-week period. The study consists of Pre-screening (Visit −1), Baseline (Visit 1), a 2-week Treatment Period (Visits 1-10), a 16-week Washout Period, an Interim Assessment (Visit 11), a second 2-week Treatment Period (Visits 12-21), and a Final Assessment (Visit 22).
Study Agent/ Intervention Description	tDCS and sham stimulation sessions lasting 20 minutes at a current intensity of up to 2mA in the targeted cortical tissue
Number of Subjects	20
Subject Participation Duration	28 weeks: 2 weeks of tDCS/sham, followed by a 16-week washout, followed by 2 weeks of tDCS/sham, followed by an 8-week final assessment.
Duration of Follow up	None
Estimated Time to Complete Enrollment	18 months
Statistical Methodology	The collection of **pilot data** from this study will provide initial estimates of the variability and the effect sizes. This information will then be used for the more formal calculations of power and sample size necessary to conduct a pivotal trial. All future statistical testing will use repeated measures ANOVA once a large enough sample is reached.
Safety Assessments	Data safety monitoring board meetings will be scheduled to monitor progression of the study and review drug adverse events
Efficacy Assessments	(i) Consent rate and treatment completion rate (ii) Statistically significant differences between baseline and post- tDCS stimulation performance on a series of language metrics.
Unique Aspects of this Study	This is the first study to evaluate the efficacy of HD-tDCS for the treatment of language deficits of lvPPA, a neurodegenerative and progressive condition with no known effective treatment. It would also be the first study to access whether HD-tDCS can increase brain functional connectivity and regulate abnormal patterns of neuronal frequencies and synchronizations in this patient population.

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1. STUDY OBJECTIVES

The logopenic variant of Primary Progressive Aphasia (lvPPA) is an untreatable neurodegenerative disorder that is often referred to as the 'language form' of Alzheimer's Disease (AD). Transcranial Direct Current Stimulation (tDCS) has emerged as a safe and potentially effective tool that appears to enhance language production when delivered during language training (Tippet et al., 2015). This technology provides a critical opportunity to conduct disease intervention. In this study, we **will test our hypothesis that High-Definition tDCS (HD-tDCS) will improve performance on language tasks by increasing functional connectivity and by regulating abnormal neuronal oscillatory patterns.** The rationale for this project is that a determination of the therapeutic efficacy and the associated neural mechanisms of HD-tDCS in lvPPA is likely to offer a scientific framework whereby new stimulation parameters, conditions, and target sites can be deciphered.

1.1. Justification of Selecting lvPPA Subjects for HD-tDCS Treatment

The sparse number of studies done so far presuppose a conceptual framework predicated on the idea that because of relatively widespread neurodegeneration, these patients do not remap language functions to novel networks, but that instead they continue to use pre-existing neural areas with declining efficiency (Rogalski et al., 2011). This stands in contrast to the working models for post-stroke aphasia recovery where the assumption is that patients will engage in the recruitment of unaffected brain areas as an important compensatory mechanism (Abel et al., 2015). The aforementioned 'neurodegeneration' model would suggest that in the case of lvPPA an appropriate neuromodulation approach would lead to the tailored and narrow stimulation of disease-specific affected brain regions. Notwithstanding the biological plausibility of this model, all the published studies on lvPPA and other PPA subtypes have used conventional tDCS montages, a method incapable of focally targeting specific brain regions. High-Definiton tDCS (HD-tDCS) on the other hand, is a recently developed system that allows for more focal stimulation based on increased current focality and intensity (Villamar et al., 2013). What remains lacking is knowledge of the therapeutic efficacy and neural mechanisms of HD-tDCS when used in lvPPA. There is, therefore, a critical need to evaluate the effects on language performance and the underlying neural mechanisms of active HD-tDCS aimed at the left posterior temporo-parietal cortex (TPC), the most consistent neural correlate of this condition (Gorno-Tempini et al., 2011). Without such information the promise of disease-specific and personalized tDCS procedures for the treatment of this neurodegenerative aphasia will likely remain limited.

1.2. Objectives

To determine whether active HD-tDCS targeting the dominant posterior TPC can improve language performance, increase language network functional connectivity, and improve abnormal patterns of resting state neuronal frequencies and synchronizations.

Specific Aim 1. Determine changes in language performance after 10 HD-tDCS stimulation sessions (QD) lasting 20 minutes at a current intensity of up to 2mA in the left TPC in a randomized, double-blind, sham-controlled, within-subject cross-over study with 20 lvPPA subjects ages 45 years and greater.

Specific Aim 2. Determine the effects of the conditions described in specific Aim 1 on the resting state Language network-level changes in left TPC functional connectivity between the conditions described in Specific Aim 1.

Specific Aim 3. Determine the effects of the conditions described in Specific Aim 1 on the neuronal frequency distribution and connectivity measures associated with the left TPC as assessed by MEG.

1.3. Outcome Measurements

The following outcome measurements will be used to test our proposed hypothesis:

- **Primary outcome measures:** Language performance as assessed at baseline and post-stimulation procedure (time frame: 2 weeks)
- **Secondary outcome measures:** Language network resting state changes after stimulation procedure (time frame: 2 weeks)
- **Tertiary outcome measures:** Resting-state neuronal frequencies and synchronizations changes after stimulation procedure (time frame: 2 weeks)

1.4. Impact of the Proposed Study

Currently, no FDA-approved therapy exists for lvPPA despite it being the most prominent cognitive impairment in approximately 27% of patients with early onset Alzheimer's Disease (Mendez et al., 2012). If this mechanistic approach is successful, we will lay a conceptual framework for the future development of optimal neuromodulation avenues for the rehabilitation of multiple neurodegenerative aphasias and other related conditions. We hope the technique will effectively enhance language production for this population.

2. BACKGROUND AND SIGNIFICANCE

2.1. Background

lvPPA is a neurodegenerative condition with no known effective treatment despite its relatively common occurrence in patients with AD and its associated catastrophic effects on work and home life. The disorder is typically characterized by word retrieval difficulties, word and sentence repetition deficits, and overall, by a type of language impairment that leads to a disturbance of the phonemic buffer for words (Meyer et al., 2015). Alzheimer's disease is the most common underlying neuropathology, and in accordance with the role of the posterior perisylvian region in phonological processing (Pillay et al., 2014), focal degeneration of the dominant posterior TPC is the most frequently identified pattern of brain involvement (Gorno-Tempini et al., 2008).

With the advent of tDCS as a promising therapeutic and rehabilitation tool in both post-stroke and neurodegenerative aphasias, it seems likely that these conditions will differ in their optimal neuromodulation approach as a direct result of their distinct underlying pathophysiologic mechanisms: Stimulation of spared perilesional and contralateral areas in the former, and of disease-specific and growingly inefficient brain regions in the latter. Our overall scientific premise is strongly supported by the existing scientific literature, with stroke-related studies showing major neuroanatomical reorganization after the initial injury (Dancause et al., 2005; Abel et al., 2015), and PPA studies revealing early reductions in language-specific effective connectivity and relatively rapid neurodegenerative changes, two findings consistent with the absence of any major reorganizational changes of brain functional networks (Sonty et al., 2007; Rogalski et al., 2011). Despite the soundness of the previously discussed models, all published studies of tDCS in PPA have relied on the broad stimulation of left hemispheric structures using conventional montages, and none of them have sought to use HD-tDCS to focus the stimulation on the more discretely affected brain areas that typify the different PPA variants. (i.e. left TPC in lvPPA, the left Inferior Frontal Gyrus (IFG) in the non-fluent/agrammatic variant, and the left temporal pole in the semantic variant). Correspondingly, an additional element of our overall scientific premise is the fact that HD-tDCS as a technique, can increase current focality and intensity (Datta et al., 2009; Muthalib., 2017). This focality is robust to tissue (modeling) parameters (Datta et al., 2012), and clinical neurophysiological studies have confirmed the focal current delivery (Edwards et al., 2013). Even though no published literature exists on the use of HD-tDCS in the PPA population, its feasibility, tolerability, and its non-inferiority to tDCS have been documented in patients with chronic post stroke aphasia (Richardson et al., 2015). HD-tDCS has also been shown to produce longer lasting after-effects when compared to conventional tDCS (Kuo et al., 2013), and others have already speculated about its potential role in the rehabilitation of neurocognitive impairments resulting from localized brain injury (Hogeveen et al., 2016).

Despite its promise for the treatment of PPA, knowledge of its mechanism of action and a demonstration of its therapeutic effectiveness in this population are still critically needed. In the absence of such knowledge, realization of the therapeutic potential of this cutting-edge technique will likely remain difficult, not only in the case of PPA, but also for the treatment and rehabilitation of other related neurodegenerative conditions.

2.2. Significance

If this mechanistic study succeeds, we will be able to **1)** provide conceptual proof that language performance can be improved by targeting specific dysfunctional neural networks during the clinical phase of disease. **2)** determine whether stimulation intervention reaches specific neural network targets and assess the network level responses; **3)** predict if the network activity modulation can concurrently improve language performance; and **4)** provide essential information needed to prepare future pivotal device trials.

3. RATIONALE

3.1 Scientific Premise

Aim #1. Evaluate the therapeutic efficacy of HD-tDCS. Anodal (positive) tDCS appears to increase both the amount and the speed of learning by promoting mechanisms of long-term potentiation (Fritsch., 2010). From a behavioral perspective, these changes in synaptic activity seem to outlast the initial period of stimulation only when the stimulation is delivered 'online' during a behavioral training task (Monti et al., 2008; Baker et al., 2010; Marangolo et al., 2013), and when compared to the 'offline' method, only 'online' tDCS was capable of reducing vocal response times in a study of elderly adults (Fertonani., 2014). These findings are in support of a pivotal part of our scientific premise: that 'online' HD-tDCS is preferable in elderly persons with aphasia.

Only a small number of tDCS studies exist in the the PPA population; some excluded the lvPPA subpopulation altogether (Cotelli et al., 2014; Teichmann et al., 2016) and another included lvPPA patients, but with what we believe are relative weaknesses in its design: The use of a conventional tDCS montage without individualized modelling of current delivery, the use of a 'locked' target site without consideration of the specific PPA variant at hand, and a relatively short 2-month "wash out" period as evidenced by the persistence of behavioral gains at the 2-month follow up (Tsapkini et al., 2014). An additional small number of studies that included lvPPA patients have been published, all of them relying on the use of conventional tDCS, a single stimulation target for all PPA subtypes, or the absence of a sham condition for comparison (e.g. McConathey et al., 2017; Hung et al., 2017). Based on the support from the discussed studies our scientific premise is that tDCS when combined with language training interventions can improve language performance in PPA. Neverthessless, what remains unknown are the effects of using 'online' HD-tDCS when tailored to each PPA variant and guided by the individualized modelling of target sites.

Aim # 2. Identify the effects of HD-tDCS on language network functional connectivity. We hypothesize that tDCS is able to modulate abnormal neuronal processing in patients with aphasia as measured by fMRI. This premise is supported by a recent study of post-stroke aphasia in which patients named pictures of common objects during fMRI and concurrently received anodal or sham stimulation to the left primary motor cortex. In this experiment anodal tDCS selectively enhanced the activity in a larger language-related network, but not in other task-related components (Darkow et al., 2017). Of note, the authors themselves mentioned that the use of conventional tDCS (and not HD-tDCS) made it impossible to dissect the exact source of the neural modulation.

In the specific case of PPA, all PPA syndromes are associated with distinctive functional neuroanatomical profiles of abnormal language processing relative to healthy older individuals (Hardy et al., 2017). The syndromic signatures found in this particular study were in accord with prior predictions and as expected, the logopenic variant was characterized by decreased activation of the posterior superior temporal cortex that correlated with performance on post-scan behavioral testing. What remains lacking is knowledge of the effects of tDCS in general, and HD-tDCS in particular, on measures of brain functional connectivity in the PPA population.

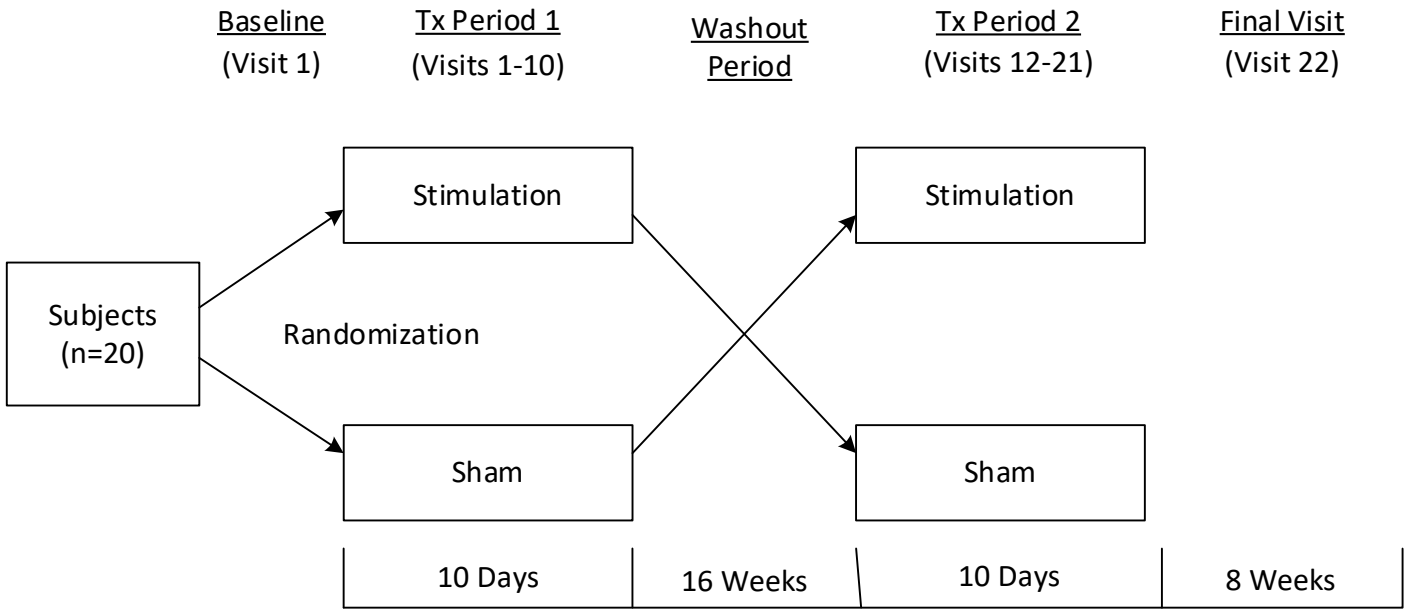
Aim # 3. Determine the effects of HD-tDCS on spontaneous neuronal oscillatory pattterns. tDCS can reshape brain networks and increase global connectivity in healthy adults as measured by MEG (e.g. Garcia-Cossio et al., 2016). In the case of PPA a recent MEG study demonstrated a distinct spatiotemporal pattern of altered functional connectivity that was unique to each individual variant (Ranasinghe et al., 2017). What remains to be elucidated is the effect that HD-tDCS has on these neurophysiological signatures of network-specific neuronal dysfunction.

4. STUDY DESIGN

4.1. Overall Design

This study will test our hypothesis that HD-tDCS will improve performance on language tasks by increasing functional connectivity and by regulating abnormal neuronal oscillatory patterns. The language performance and functional connectivity changes will be determined in a randomized, double-blind, sham-controlled crossover manner, in which a stimulation of up to 2mA in the targeted cortical tissue or sham is administered to 20 lvPPA subjects age 45 years and older. The order of treatments is counterbalanced in a within-subject crossover design, as illustrated in Fig. 2 below. In brief, study participants will receive sham during one treatment period and stimulation during the other treatment period.

Figure 2. Study Design and tDCS Treatment Protocol



The Screening Visit includes medical history, Language Assessment battery, MRI safety screening, and TMS Neuronavigation. Visit 1 (Baseline) will include fMRI and MEG. Additionally at Visit 1, and for 9 additional days in a two-week period (Tx Period 1), each subject will undergo real stimulation or sham and simultaneous word and non-word reading and repetition tasks. At the end of Tx Period 1, a 16-week washout period begins. After the first 8 weeks of the 16-week washout period, subjects return for Assessment Visit 1 where they receive the Language Assessment battery, including the reading and non-word repetition tasks tested at baseline, and 'trained' during each of the stimulation sessions. After the 16-week washout period, Tx Period 2 begins. Subjects undergo stimulation or sham and the simultaneous word and non-word reading and non-word repetition tasks for 10 days over a two-week period. Eight weeks after the end of Tx Period 2, subjects receive the Language Assessment Battery at Assessment Visit 2, which is the last study visit.

An unblinded member of the study team having no contact with the study subjects will randomize them to the treatment conditions, while the language assessment battery of tests will be delivered by a blinded member of the study team. The language training exercises used during each tDCS session as well as the tDCS intervention itself will be delivered by a blinded, qualified and formally tDCS-trained member(s) of the study team.

Data safety is monitored by three data safety monitoring board (DSMB) members who are not related to the study.

4.2. Inclusion and Exclusion Criteria

Inclusion Criteria

- Diagnosed with lvPPA subtype, defined as either clinical lvPPA or imaging-supported lvPPA in accordance with the most recent diagnostic criteria (Mesulam., 2001; Gorno-Tempini et al., 2011).
- Fluent in English.
- 45 years of age or older (Individuals with lvPPA are extremely rare below this age cut-off).
- Structural brain MRI done within the 3 years prior to enrollment.

Exclusion criteria

- Severe cognitive, auditory or visual impairments that would preclude cognitive testing.
- Presence of major untreated or unstable psychiatric disease.
- A chronic medical condition that is not treated or is unstable.
- The presence of cardiac stimulators or pacemakers
- Any metal implants in the skull
- Contraindications to MRI
- History of seizures
- History of dyslexia or other developmental learning disabilities.

4.3. Subject Recruitment

To enroll a total of 20 study participants, we anticipate pre-screening and approaching about 50 lvPPA patients who are seen in the MCW Neurology clinics and the MCW Geropsychiatry clinic for standard care. These patients will range in age from 45–85 years. Recruitment efforts will be conducted exclusively in the MCW Neurology and Geropsychiatry clinics initially but may be expanded to include the greater metropolitan Milwaukee, WI area if needed. The Medical College of Wisconsin (MCW) Dementia Research Team has extensive experience recruiting patients from the clinic and the Milwaukee community, using flyers, press releases, and community presentations.

5. STUDY VISITS AND PROCEDURES

5.1. Schedule of Visits

A **screening (Visit -1)** session will be conducted. This could take place after a routine clinic visit, or by phone, to perform the Informed Consent (IFC) discussion, review inclusion criteria, collect demographics and basic medical history, and begin MRI safety screening. The Language Battery will also be completed as part of the screening visit. Additionally (in the case of those meeting criteria), patients might visit the Tosa Health Center or Medical College of Wisconsin for stimulation planning. This would entail the use of a Transcranial Magnetic Stimulation (TMS) neuronavigation system. The Language battery and TMS can occur on two separate days prior to the first treatment visit of Treatment Period 1. Subjects will also be invited to **baseline (Visit 1**). At baseline, the study team will complete fMRI and MEG scans and randomize participants to a treatment group. Procedures within Visit -1 and Visit 1 may be completed in any reasonable order, and may overlap, up to 3 months prior to the first treatment visit of Treatment Period 1. At **Visit 1**, subjects will receive tDCS while simultaneously completing the reading and repetition "trained tasks. Subjects will then return for 9 additional **treatment sessions (Visits 2-10)** where they will receive stimulation or sham, along with trained task administration**.** At **Visit 10**, subjects will receive MRI, MEG scans, and the Language Battery. These procedures may be completed one month after the last treatment session of Treatment Period 1**.** At 8-weeks from the last Treatment Period 1 visit, subjects will return for the first **assessment session** (**Visit 11**), in which the Language battery, including the trained tasks will be repeated. Subjects will then return 8 weeks later to begin the second series of treatments (**Treatment Period 2, Visits 12-21)** and receive MRI, MEG, and Language Battery on visits 12 and 21. MRI, MEG, and the Language battery will be completed no greater than 3 months prior to the first treatment session of Treatment Period 2, then again no greater than one month after the final treatment session of Treatment Period 2. At each visit during Treatment Period 2, subjects will receive the cross-over treatment (either sham or stimulation) while simultaneously completing the reading and non-word trained tasks. The final

assessment session **(Visit 22)** will be conducted 8 weeks post Treatment Period 2. The Language battery, including the trained tasks, will be repeated at this final study visit.

Refer to Table 1 for a schedule of study procedures.

5.2. Subject Retention and Compensation

Contact by telephone will be maintained with the subjects during the 16-week washout period. Subjects will be contacted at weeks 4, 8, and 16 of the wash-out period. During these calls, the study coordinator will inquire about potential adverse events (AE) and remind subjects about their 8-week assessment visit and first Tx Period 2 visit. Telephone contact will also be maintained during the 8-week period between the end of Tx period 2 and the final assessment. Subjects will be contacted 4 and 8 weeks after Tx period 2. During these calls the study coordinator will inquire about potential AE and remind subjects about their 8-week final assessment. The study staff will follow the data and safety monitoring plan described below to monitor AEs.

Subjects will be compensated for participation in the study. We will pay no stipend for the screen visit, $30 for visits 1, 10, 12, and 21, $7 for visits 2-9 and 13-20, and $17 for visits 11 and 22. The total stipend if all visits are completed is $266.

Subjects may be reimbursed for any reasonable travel expenses as needed to attend study visits. If subjects live 25 miles or more one way from the study site, they will be reimbursed at the standard MCW travel rate of $0.56/mile.

If a study visit requires an overnight stay, subjects will receive a $25 meal reimbursement per night.

Subjects may be eligible to lodge at Kathy's House if they reside at a permanent address 50 miles or greater from Milwaukee. Kathy's House is located on the Froedtert Hospital campus and provides housing for research subjects who require a stay greater than 3 days.

Payment for lodging at Kathy's House will be arranged and covered by the study team. Care givers are expected to lodge with subjects to the extent possible.

With the subject's verbal consent, a referral can be sent by the study team to Kathy's House. The following personal information will be included in the referral to Kathy's House: subject and care giver name, date of birth, gender, city, state, zip code, phone number, email address, and reason for visit.

Upon reception of the referral, Kathy's House will conduct a formal background check using TruthFinder.com. The subject and caregiver's names and birthdates will be used to check for any criminal charges associated with either person. Kathy's House has the right to reject any referral based on this background check.

The study team does not plan to reimburse for any other type of lodging.

5.3. Early Termination Visit

If a subject decides to exit the study, a termination visit will be scheduled. This will include all Language assessments normally performed at assessment visits. In addition, any incidental imaging findings will be addressed.

5.4. Study Procedures

5.4.1. Informed Consent

Participants will provide written informed consent at the Visit -1. When feasible, informed consent will be obtained right after a routine clinic visit. The consent process will involve distributing a full consent form to the potential study participant and a thorough presentation of the purpose and risks of the study, and an explanation of study procedures by the staff member obtaining consent. Sufficient time for questions, discussion, and the subject's decision will be allowed for proper informed consent by the participant. Once the participant fully understands the study protocol as outlined in the consent form, he/she will acknowledge his/her consent with a signature that

is placed directly below the text on the consent form. Each participant will receive a complete copy of the signed consent form for his/her personal records. The study coordinator will keep the original signed copy for study records.

5.4.2. Demographics, Medical History, and MRI Safety Screening

Demographic information, basic medical history, and MRI safety screening begin at the screening visit and are completed at baseline prior to any study participation by the subject. Data are collected from participants including demographic information (age, gender, race, ethnicity), medical and surgical history, hospitalization history, medications and supplements, and family history of illness. We will also ask questions pertaining to fluency in languages, education, history of dyslexia or other developmental learning disabilities, and work history.

5.4.3. Transcranial Magnetic Stimulation (TMS) neuronavigation

The TMS can be used to determine optimal electrode positioning. Each patient's individual head and brain anatomy can be modeled along with a de-identified structural brain MRI obtained prior to the visit. Once optimal electrode positions are determined, the patient's structural MRI and the coordinates of the electrode positions will be uploaded into a neuronavigation software; the electrode positions can be converted into 3D spheres, which can then be loaded into the software. The neuronavigation software comes equipped with automatic segmentation algorithms that allow cortical and surface (3D curvilinear and skin) reconstructions based on the patient's raw structural MRI. The electrode locations are then overlaid onto the reconstructed curvilinear brain.

5.4.4. Language and Cognitive Assessments and Language Tasks

Picture naming. A standardized set of 160 pictures will be tested (80 for each treatment period). The pictures are black and white drawings executed according to a set of rules to provide consistency of pictorial representation. Pictures will be presented on a computer screen and at the start of the task patients will be asked to name carefully and consistently. Each picture will be presented for a period of up to 10 seconds, and answers will be digitally recorded for later transcription and scoring. Approximate total time will be 10 minutes. With this test we seek to detect changes in spontaneous word production resulting from the tDCS stimulation procedure. (Snodgrass & Vanderwart.,1980).

Alternatively, we will use the Neuropsychological Assessment Battery (NAB) naming sub-test. The NAB naming sub-test involves showing the examinee color photographs of objects, as opposed to black and white line drawings. The NAB naming test has fewer items (31), and all items are administered to test-takers, with no setting of a basal level or discontinue criteria. Patients are allowed 10 seconds to freely recall the name of the item, and then are given 5 s after the semantic cue and 5 s after the phonemic cue, for a total of 20 possible seconds per item (Stern & White, 2003).
Approximate total testing time will be 10 minutes. 2 different versions of the test will be used (one for each treatment period).

Letter and category fluency. We will test 3 letters and 2 categories using the Verbal fluency test from the Delis-Kaplan Executive Function System (Delis et al., 2001a). This subtest will require the individual to randomly generate words based on given parameters such as words beginning with the letter *F*. This test is based on the original FAS verbal fluency test. The test builds upon this by including a semantic fluency test that requires generating boy's names and animal names.
Estimated testing time: 6 minutes.

Digit span test. Auditory attention span and working memory will be assessed using the digit span forward (DSF) and digit span backwards (DSB) subtests of the Wechsler memory scale –Fourth edition (Benson et al., 2010). The task was chosen due to its reliance on phonological short-term memory (STM), a function often impaired in lvPPA (Meyer et al. 2015). With this test we seek to detect changes in phonological STM resulting from the tDCS stimulation procedure.
Estimated testing time: 5 minutes.

Phonological Short-term Memory Test. This test assesses the capacity to retain speech sound information in a short-term memory store across a 5-second maintenance interval. The material is presented in the form of

digitally recorded natural utterances by a single talker, with syllable trains containing 1-5 syllables (24 trials per length condition). Participants will be asked to identify: same pairs = first train followed by a different recording of the same items, versus different pairs = first train followed by a train differing in a single syllable. Testing will include a total of 120 items (60 for each treatment period), and responses will be selected by the patient using a touch screen system (Pillay et al., 2017). This experimental measure complements the more standard Digit Span test by assessing phonological short-term memory without the articulatory demands of the Digit Span test.
Estimated testing time: 10 minutes.

Word and non-word rhyme matching. This test assesses the ability to mentally access the sound of a printed word (Pillay et al., 2014) or nonword (Pillay et al., 2017, 2018) prior to articulation. Each trial consists of a sample word or nonword presented in the center of a computer display with two similar choice items below the sample. The patient's task is to select the item that rhymes with the sample. Trials are constructed such that phonologic similarity is uncoupled from orthographic similarity (e.g., does *snow* rhyme with *plow* or *blow*).
Word rhyme matching: 40 word-triads (20 for each treatment period). 20 regular word triads with all regular words, and 20 irregular word triads with one irregular word.
Nonword rhyme matching: 72 triads of word-like nonwords (36 for each treatment period). Matched on length and orthographic neighborhood size with the word triads used in the word rhyme matching portion.
Estimated testing time: 10 minutes.

Spontaneous Speech Sample. This task consists of picture description from the Boston Diagnostic Aphasia Examination ("Cookie Theft Picture"), in which the participant is asked to "Tell me everything you see going on in this picture." Responses will be digitally recorded and later transcribed and analyzed. Since diagnostic criteria for lvPPA includes changes to spontaneous speech, obtaining an objective measure of discourse can detect subtle changes to speech and language that may be clinically meaningful (Ahmed et al., 2012; Wilson et al., 2010). Specifically, through automated analyses we will measure semantic content, speech fluency, and timing measures such as words-per-minute (Ahmed et al., 2013; Mueller et al., 2017).
Estimated testing time: 4 minutes.

Alternatively, we will use the oral production sub-test of the NAB. This sub-test uses a speech output task in which the examinee orally describes a picture of a family scene (Stern & White, 2003). 2 different versions of the family scene will be used (one per treatment condition).
Estimated testing time: 4 minutes.

Reading Comprehension. We will use the reading comprehension sub-test of the NAB. A two-part sub-test that requires the examinee to demonstrate reading comprehension of single words and of sentences by pointing to multiple choice sentences that match the visual stimuli (Stern & White, 2003). 2 different versions of the test will be used (one for each treatment period).

Montreal Cognitive Assessment (MoCA). MoCA is a widely used screening assessment for detecting cognitive impairment. It is a one-page 30-point test administered in approximately 10 minutes (Nasreddine et al. 2005). 3 different versions of the test exist in English, and 2 will be used for each patient (one per treatment condition).

'Trained' tasks. This includes items tested at baseline and after treatment periods, with half of them also practiced (i.e. trained) during all stimulation procedures (either sham or real tDCS). It will include the reading of words and non-words and the repetition of non-words (approximately 480 items, a total of 288 items for reading and 192 for repetition, divided across two treatment periods). Non-word tasks were selected due to their reliance on the kind of phonologic mechanisms subserved by the dominant temporo-parietal cortex and impaired in lvPPA (Pillay et al., 2017). We will test vocal reaction times and the data will be analyzed using a Matlab custom script.
Estimated testing time: 25-30 minutes.

5.4.5. Neuroimaging Assessments

The acquisition strategy for lvPPA participants is to collect datasets that include resting-state functional MRI (rs-fMRI), diffusion MRI (dMRI), and resting state magnetoencephalography (rsMEG).

MRI Acquisition Protocols
All lvPPA patients will undergo four 60-minute 3T MRI scanning sessions (total 4 hrs), including high-resolution T1 and T2 structural MRI, dMRI, and rs-fMRI as summarized below. In the case of left handed participants (approximately 80% are left hemispheric dominant), they will undergo a quick fMRI test (~ 6 min) to confirm their left hemispheric dominance (Binder et al. 1995).

3T MRI Hardware: Scanning will be done on GE MR 750 3T clinical scanners (50 mT/m & 200 T/m/s gradients) with a Nova 32-channel neuroimaging phased array receive head coil and whole-body rf transmission.

3T MRI Pulse Sequences: fMRI and diffusion MRI acquisitions will use prototype GE pulse sequences from the "ProtoPak2" software package, made available to us by a research agreement with GE. These state-of-the-art sequences provide multi-band acquisition of fMRI and dMRI data, greatly accelerating the acquisitions and allowing reductions in voxel size and repetition time to match those of the HCP protocol.

Resting-State FMRI (rs-fMRI) Protocol. The rs-fMRI parameters will be identical to the HCP Lifespan protocol, including an eyes-open fixation task, 30 minutes of rs-fMRI data divided into six 5-minute runs, and a 50:50 alternation of phase encoding direction.

Structural MRI Protocol. T1-weighted structural images will be acquired using the GE "BRAVO" pulse sequence and "Cube" with "ARC" for T2-weighted images, which is a 3D fast spin echo sequence using GE's autocalibrated parallel imaging technology. These vendor-supplied sequences provide comparable image quality to those of the HCP at the same 0.8 mm isotropic voxel size.

Prior to fMRI scans, subjects will undergo MRI safety screening and, as detailed in sections 7.3. and 7.4., respectively.

MEG Acquisition Protocol
MEG offers relatively good spatial localization of neural activity sources together with millisecond temporal resolution not possible with hemodynamic imaging methods. All lvPPA patients will undergo resting state MEG recordings.

Our MEG is a Vectorview whole-head 306-channel system (Elekta Neuromag Ltd., Helsinki, Finland) that combines 102 magnetometers with 204 planar gradiometers. MEG Data will be acquired at 2000Hz with a 650Hz antialiasing lowpass filter. Patients will be in the supine position and will focus on projection screen displaying a fixation crosshair. The recording protocol for rs-MEG will follow those of the Human Connectome Project.

Continuous Recognition Memory task, (CRM task): To be performed during MEG acquisition. The stimuli consist of 5 target words and 40 distractor words repeated in 4 consecutive blocks, which are read by a digitized native English speaker. The auditory stimuli will be presented using E-Prime 1.2 software (Psychology Software Tools, Pittsburgh, PA) and delivered binaurally to the patient using Tubal Insert Earphones (TIP-300, Nicolet Biomedical, Madison, WI). Prior to the start of the MEG recording, the 5 target words will be presented to the patient several times. During the language task patients keep their eyes open and maintain visual fixation on a small square presented on a screen while listening to the words. Patients are instructed to lift an index finger when they recognized a target word. Alternatively, we may ask the patients to press a button in order to document responses (Raghavan et al. 2017).
Approximate duration: 30 minutes.

5.4.5. Randomization, Treatment Dosing and Administration
An unblinded member of the study team will randomize participants to the treatment conditions. Study Group assignment will be based on random number generation (in blocks of 4) followed by the creation of numbered envelopes.

In Tx Period 1, study participants will receive either stimulation (up to 2 mA in the targeted cortical tissue) or sham; in Tx Period 2, all subjects will crossover and receive the other treatment. This is a double-blind study, so

both the participants and the study team members involved in language training, tDCS delivery, and assessment of outcomes will be blind to the treatment received.

The Soterix MXN-9 High-Definition stimulator will be used for focal current delivery; this device is currently housed at the 'Computational Neuroscience and Neurotechnology lab' at MCW **(See Images 1 and 2).**

Images 1 and 2*: To the left* ***(Image 1)****, 9-channel HD-tDCS device (MXN-9, Soterix Medical Inc.). To the right* ***(Image 2),*** *Soterix Medical HD-Cap showing 4 X 1 High Definition montage.*

When conducting HD-tDCS, specially designed insets, electrodes, stimulation protocols, and conductive gels will be used. Appropriate instrumentation, electrode design, and protocols are considered important for HD-tDCS safety and comfort. All materials were purchased from Soterix Medical (New York, USA). A flexible plastic EEG cap or a latex swim cap will be placed on each participant's head. The EEG cap will be held in place with a chin strap and if using a swim cap, the latex material snuggly fits the participant's head without a strap. To guarantee individualized targeting of the left posterior TPC, we will follow the steps below with minor variations as required:

1) The Soterix HD-Targets and/or HD-Explore software programs can be used to determine the optimal electrode positioning and stimulation current based on the identified brain target and the subject-specific predicted current flow. For this purpose, each patient's individual head and brain anatomy can be modeled by Soterix Medical (prior to visit using the de-identified structural brain MRI obtained prior to enrollment as part of routine, clinical standard of care **(see Image 3).** There are freely available software packages such as SimNIBS 2.1 (Saturnino et al., 2018 bioRxiv) that can also be employed for individualized current modeling. We will explore these alternative packages to determine the electrode positions and for current flow simulations. Guidelines from prior HD-tDCS modeling studies (Alam et al., 2016) will also be considered for improving the focality of stimulation.
2) Once optimal electrode positions are determined, the patient's structural MRI and the coordinates of the electrode positions will be uploaded into a neuronavigation software; the electrode positions can be converted into 3D spheres, which can then be loaded into the software. The neuronavigation software comes equipped with automatic segmentation algorithms that allow cortical and surface (3D curvilinear and skin) reconstructions based on the patient's raw structural MRI. The electrode locations are then overlaid onto the reconstructed curvilinear brain.
3) During one of the pre-stimulation (baseline) visits, the cap will be fitted to the patient and using the optical tracking tools and the neuronavigation software, we will navigate to the electrode locations from the brain surface onto the patient's scalp. A permanent marker will be used to mark the electrode locations directly on the cap.

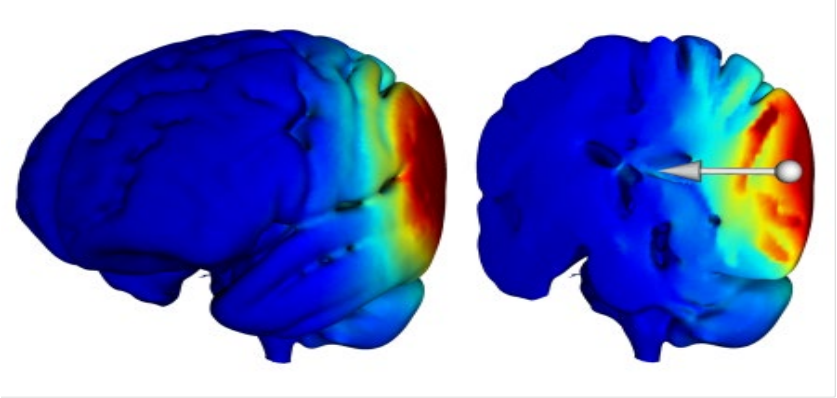


Image 3: *Visualization example of HD-tDCS current flow modeling for an individual subject's anatomy (depicted target site is the left posterior TPC, oblique view to the Left and coronal view to the Right). Heat map color corresponds to higher field intensity (modeling was done at the Computational Neuroscience and Neurotechnology lab using the Soterix Medical Neuro-Targeting Software).*

The electrode casings or holders will be secured in the cap at the marked locations. The skin prepping guidelines as listed in Villamar et al. (2013) will be followed: separating the hair inside the electrode casings until the scalp is exposed, removing hair products and dirt on the scalp using an alcohol swab and then filling the electrode casings with 3 mL of Signa Gel (Parker Laboratories, NJ) or HD-GEL™ (Soterix Medical) with more applied if needed. The electrodes will be placed on a platform inside the casings so that they are completely immersed in the gel. More gel will be applied to cover the electrodes and then they will be held in place with the casing caps. Impedance values will be examined for each of the 5 electrodes (4 X 1 montage seen on image 2) and will all be verified to be <2 quality units (Turski et al., 2017).

Stimulation sessions will consist of daily 20-min sessions with a current of up to 2 mA (sham or anodal) to the targeted cortical tissue for five consecutive days per week and for 2 consecutive weeks (10 sessions in total). The device contains a double-blind switch that can be turned to ON or OFF from the back of the device. Once the double-blind mode is turned ON, the device will not show any sham settings on the front and will not display any true current that is being delivered.

Before treatment begins, a blinded member of the study team will fit the cap, prep skin, and place and immerse electrodes into casing using gel. The blinded study team member may be a research coordinator and/or research assistant, who are trained in the theory and application of the HD-tDCS device. An unblinded member of the study team will program the device for each stimulation setting, turn the double-blind switch ON, and then leave the room. A blinded member of the team will then deliver the stimulation without knowing if it is an active session or a sham session. The safe delivery of tDCS, even by non-professional caregivers, has been previously documented (see Im et al, 2019).

Auto-sham automatically calculates and produces a sham waveform based on the indicated "real" waveform. For example, for a corresponding real waveform of 1.5 mA and 20 minutes, auto-sham will provide a ramp up/down to 1.5 mA at the start of stimulation (for 30 seconds), and again after 20 minutes with the timer automatically adjusted such that the total run time is exactly matched to the real case (Poreisz et al., 2007).

6. DATA MANAGEMENT

6.1. A secure web-based system will be used to enroll patients and obtain the randomly assigned treatment group. Data forms will be printed, completed, and entered into the database using a secure web-based application. The database will be monitored for completeness, consistency, accuracy, and timeliness. No patient-identifying information will be stored in the database. To ensure that data are secure from external violation, computer systems containing study data will be password protected, and physical access to the computer systems will be limited.

6.2. Determination of changes in Language Function and Concurrent Improvement in Network Activity.
The language and MRI/rfMRI datasets will be obtained at baseline (before sham/active tDCS administration) and on the last day of each 2-week treatment period. These two time points will be denoted t = 1, 2. The two 10-

subject groups, both of which will receive both sham and active tDCS at different treatment phase, will be denoted *g* = 1, 2. The set of Language (LG) scores for subject *s,* from group *g,* at time *t* will be denoted *LG*(*s,g,t)*, where s = 1, …, 10; g = 1, 2; and t = 1, 2. The Language-Network functional connectivity (LFC) calculated between the left posterior temporal and inferior parietal cortex for subject *s,* from group *g,* at time *t* will be denoted *LFC***(***s,g,t).*

6.3. Language Changes Due to Stimulation. Scores across all tests within the language battery will be combined into one composite measure to facilitate assessment of overall language performance across domains. All seven scores will be normalized to a *Z*-score by transforming individual raw test scores according to the mean and standard deviation of the scores for all subjects. Then, *Z*-scores of each test will be averaged to obtain an individual composite language *Z*-score (McConathey et al., 2017). We will employ age, years of education, gender, and gray matter (GM) volume as time-invariant covariates to obtain residual variables to determine the LG changes due to stimulation. We will model the LG score as a function of these nuisance regressors. This regression will be performed using all the data (i.e., all subjects, all groups, and all times):

$$\boldsymbol{\Delta LG(s,g,t) = \beta_0 + \beta_1 Age(s) + \beta_2 Edu(s) + \beta_3 GM(s) + \beta_4 Gender(s) + Res(s,g,t)}$$

Define $\widetilde{\boldsymbol{\Delta LG}}(\boldsymbol{s,g,t}) \equiv \boldsymbol{Res(s,g,t)}$. We will test the residuals $\widetilde{\boldsymbol{\Delta LG}}(\boldsymbol{s,g,t})$ using *a three-factor crossed-nested ANOVA*, with fixed factors *group* and *time*, and random factor *subject* nested within *group*. We will test for group and time main effects, as well as the group × time interaction. If we find significant main effects or interactions, we will perform post hoc procedures to determine which time and group combinations are significantly different.

6.4. Functional-Connectivity Changes Due to Stimulation. We will use the well established Human Connectome Project (HCP) fMRI processing pipelines implemented by Dr. Binder's group at MCW, which include state-of-the-art noise removal, spatial normalization, and surface-based cortical parcellation methods.

Functional connectivity matrices will be computed by first parcellating the brain into multiple regions of interest (ROI), averaging the preprocessed fMRI signal over each ROI, and then computing the *Z*-transformed correlation coefficient between every ROI pair. The functional connectivity of a number of different parcellation schemes will be examined. This includes anatomical atlas based parcellation, such as the Harvard Oxford atlas, a validated probabilistic atlas implemented in FSL that divides each hemisphere into 56 regions corresponding to portions of cortical gyri and subcortical gray matter nuclei; combined anatomical and functional parcellation of regions that tend to co-activate during resting state, as implemented in Statistical Parametric Mapping (Tzourio-Mazoyer, N., et al., 2002) and purely functional delineations such as the Crad-200, a constrained spectral clustering of resting state fMRI data into 200 parcels encompassing both cortical and subcortical regions, and a high model order Independent component analysis (ICA), as advocated by HCP investigators. Targeted exploration of connectivity driven by current understanding of the pathophysiology of lvPPA will also be pursued.

We will employ age, years of education, gender, and gray matter (GM) volume as time-invariant covariates to obtain residual variables to determine LFC changes due to stimulation. We will model the L*FC* as a function of these nuisance regressors, using the following multiple linear regression equation, and retain the residuals as $LFC^{+}_{Res}(s,t)$ for further analysis:

$$\boldsymbol{LFC(s,t) = \beta_0 + \beta_1 Age(s) + \beta_2 Edu(s) + \beta_3 GM(s) + \beta_4 Gender(s) + Res(s,g,t)}$$

where $\widetilde{LFC^{+}}(s,g,t) \equiv Res(s,g,t)$. This regression will be performed using all of the data (i.e., all subjects, all groups, and all times). We will test the *residuals* $\widetilde{LFC^{+}}(s,g,t)$ using *three-factor crossed-nested analysis of variance (ANOVA)*, with fixed factors of *group* and *time* and a random factor of *subject* nested within *group* (i.e., all subjects will be tested at all times, but the sham and stimulation groups will contain different treatment phases. We will test for both group and time main effects, as well as for the group × time interaction. If we find significant main effects or interactions, we will perform post hoc procedures to determine which time and group (i.e., sham Vs. stimulation) combinations are significantly different.

6.5. Prediction of Changes in Correlation Between LFC and LG Before and After tDCS. A multiple linear regression is used to model LG as a linear function of LFC and test the difference in slope and intercept between the active stimulation and sham groups. If the subject is in the active stimulation group, **A**(**s**,**g**) = 1; if the subject is in the sham (placebo) group, **A**(**s**,**g**) = 0.

$$\boldsymbol{LG(s,g) = \beta_{0,0} + \beta_{0,1}A(s,g) + \beta_{1,0}LFC(s) + \beta_{1,1}LFC(s)A(s,g) + Res(s)}$$

Here, **LFC(s)** represents baseline LFC for subject *s* (for simplicity, nuisance regressors are not shown).

6.6. Changes in Spontaneous Neuronal Oscillatory Patterns and synchronizations due to Stimulation

The rsMEG datasets will be obtained at baseline (before sham/active tDCS administration) and on the last day of each 2-week treatment period. For data analysis we will use the well established Epilepsy Connectome Project (ECP) MEG methods, currently used at MCW. A scalp digitization will be generated during each session of the MEG procedure that includes anatomical landmarks and localizer coils. The MEG data will be co-registered to the MRI using a minimization of the distance from the digitized headshape to the MRI derived scalp surface. The localizer coils will provide the position of the patients head relative to the MEG sensors. Sensor level activity will be projected to the cortical surface using minimum norm based spatial filters with anatomical priors. The cortical surface will be downsampled to approximately 8000 vertices; the orientation and location will act as priors on solving the transformation from sensor space to source space, known as the inverse solution. Data from the cortical surface will be spatially averaged over the anatomical parcellations. These parcellated timeseries will be used to calculate band-limited connectivity measures. Targeted exploration of connectivity driven by current understanding of the pathophysiology of lvPPA will also be pursued.

Connectivity between all ROI-pairs will be calculated in the theta (4-8 Hz), alpha (8-12 Hz), beta (13-30 Hz), and low-gamma (30-55 Hz) frequency bands using three different metrics: coherence (COH), phase lag index (PLI), and debiased weighted phase lag index (d-wPLI). Mean connection strengths within 3 intra-hemispheric language-specific ROI-groups, and those between all intra-hemispheric ROIs will be computed. We will also compute mean connection strengths between language ROI-groups and all remaining brain ROIs, and those between each hemispheric ROI and all other brain ROIs.

The same multiple linear regression models used for the analysis of rsfMRI data will be used for the analysis of rsMEG data (for simplicity, regression equations are not shown). See above for details.

6.7. Expected Results, Deliverable, and Problems

Through this study, we expect to realize two goals: ***Scientifically,*** we will demonstrate that active HD-tDCS can increase language-network functional connectivity and improve abnormal patterns of resting state neuronal frequencies and synchronizations. ***Clinically,*** we expect that the changes in network activity after the 2-week stimulation period will lead to language improvement. This study can provide conceptual proof for a rehabilitation intervention. In addition, this study will provide information and address the power of adequate enrollment, protocol adherence, subject retention, and safety for future pilot and pivotal trials.

6.8. Data Sharing

Subjects will provide written informed consent via an addendum consent form, noting their permission for the study team to share all data collected throughout their participation in the study with UW-Madison collaborator

Kimberly Mueller, PhD in the Department of Communication Sciences and Disorders and her team. Dr. Mueller and her team will analyze the study data and provide statistical support to the MCW study team.

The following data will be sent to Dr. Mueller in a secure and protected manner:

- Study ID number
- Dates of visits and consent
- Demographic information, such as age, year of birth, sex, handedness, race, ethnicity, educational history, and childbearing potential
- Medical history, such as medical/neurological diagnoses and medications
- Randomization information
- Adverse events
- TMS Neuronavigation data
- Performance on cognitive and language tests
- Voice recordings and speech samples
- Images from MRI scan
- Recordings from MEG scan

Once data analysis and statistical support are complete, Dr. Mueller send results back to the study team, where they will be stored for the duration of the study.

The data we provide will not contain any information that can directly identify subjects.

7. DATA SAFETY MONITORING PLAN

An appointed DSMB will discuss the ethical conduct of the trial, review event definitions and the subject ICF form, and further develop plans for monitoring the data and safety of the trial. The DSMB will meet at least annually to review the course of the trial. The DSMB agrees to communicate with institutional review board (IRB)/human subject committees to provide reassurances, as appropriate. There will be three DSMB members with the following areas of expertise:

- Neural mechanism underlining language and memory disorders.
- Neuroimaging
- Psychology of Language and Memory Loss.

7.1. Safety Plan

The safety issues in this study are related to use of HD-tDCS and acquisition of fMRI and MEG data. This study uses a well-known HD-tDCS montage at a safe dose of current. Previous studies on the safety and tolerability of tDCS have shown that a 2-mA current applied for 20 minutes is associated with no serious AEs (Brunoni et al., 2011). The AEs most often associated with HD-tDCS are not associated with long-term, deleterious effects, and instead are typically mild and transient in nature. The most commonly reported AEs are itching, tingling, mild headache, mild fatigue and localized burning sensation at the site of stimulation. (Brunoni et al., 2011). We will assess AEs using a customized questionnaire (Attachment 1). The questionnaire will be performed immediately after each tDCS session and during the phone follow-up calls scheduled between treatment periods.

7.2. MRI Safety

The MRI scanner device is a U.S. Food and Drug Administration (FDA)-cleared device for safe and noninvasive imaging of the interior of the human body. The GE MR750 MRI uses a 32-channel receive-only head coil, which is an investigational device. See below for further information on the 32-chanel receive-only head coil. The proposed MRI scans are NOT for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health, and they do not present a potential for serious risk to the health, safety, or welfare of a subject. The scanner also restricts the software from exceeding FDA safety levels. The scanner monitors the SAR for research scans just as it does for all other scans. Thus, the scanner

with the software fully engaged operates, from a technical design and functional standpoint, as a **nonsignificant risk** device in accordance with 21 CFR 812. By staying below these limits, the operating conditions of the MRI device are generally deemed, in and of themselves, to make the MRI device a nonsignificant risk device.

The Nova Medical 32-channel head coil (model number NMSC075-32-3GE-MR750) is an investigational device that is not approved by FDA for clinical use. This coil device includes multiple features for safe operation involving human studies. The 32-channel coil is designed and constructed as a receive-only detector of RF signals that are emitted by the brain following the RF excitation generated by the GE Healthcare MRI scanner, which is FDA approved. During the RF excitation by the scanner, the coil device is decoupled (made inactive) through redundant circuitry; thus, the coil device never transmits RF to the subject and, therefore, it has no impact on subject risk or safety.

More specifically, the coil design and construction include the following safety features: **1)** High-voltage breakdown (>2 kV) UL-94V0 flame retardant housing. **2)** Rugged construction to ensure safe operation in case of rough handling. **3)** Active detuning circuitry providing greater than 35 db isolation per element. **4)** High power passive detuning circuits in case primary detuning circuitry fails. **5)** Multiple common mode traps in all receive coil cables. **6)** Minimum of 5 mm spacing between coil conductors and patient contact.

Additionally, the coil was designed and manufactured under an ISO 13485 certified quality management system. As part of this quality system, Nova Medical has conducted a failure means and effects analysis (FEMA) of this product, and we feel that it is a nonsignificant risk under foreseeable normal conditions when used on the 3T GE X750 MRI scanners at MCW.

7.3. MRI Safety Screening

MCW-specific magnetic resonance (MR) safety screening procedures will be followed. All participants will be screened for medical devices, implants, and metal prior to undergoing MRI, first at the screening and baseline visits (Visits -1 and 1) and again prior to Visits 10, 12, and 22. If it is necessary to review medical records to confirm contraindication, a review of medical records (e.g., previous surgeries) will take place prior to the scheduled visit. During the screening process, participants will also be questioned about their ability to temporarily remove transdermal patches (such as birth control or nicotine patches). Women of child-bearing potential will be asked to confirm that they are not pregnant when signing the ICF. If a woman has concerns or is uncertain of her pregnancy status, she will be excluded, as the risks of an MRI scan to pregnant women are currently unknown. The risks related to an MRI are minimal for a properly administered visit. The MR technicians are trained and prepared to deal with any problems that may arise.

7.4. Incidental Findings by MRI

The study subjects to be recruited for this study are generally healthy. Sometimes, however, a few incidental abnormalities may be found in study subjects, such as brain tumors, vascular lesions, moderate to severe white matter lesion load, and other neuroradiological abnormalities that would preclude subjects from being included in the analysis, or that are clinical abnormalities requiring follow-up. These subjects will be advised to see their physicians for formal assessment. Dr. Granadillo is a board-certified neurologist at MCW. He will consult with the subjects in such cases.

7.5 Magnetoencephalography (MEG) Risks:

There are no health risks associated with MEG, but there is some risk of discomfort. During MEG recording, due to restriction of head movements and being in a small room, some people may experience an unpleasant feeling of confinement or discomfort from sitting still for a long time.

7.6. Subject Safety

Due to the duration and low dose of stimulation, we anticipate this study to present minimal risk to subjects. We do not expect frequent or severe AEs to occur. Subjects will be instructed to call the study site concerning any adverse events or illnesses that may occur. The DSMB will review the frequency and severity of any AEs. Stopping rules will be invoked for the subject and study if AEs are reported above the 5% threshold. Subject safety will be closely monitored during the study period, and individual participation in the study may be

suspended or terminated pending resolution of the AE. Safeguards to ensure subject confidentiality will consist of maintaining records in a locked cabinet in a locked room in the Department of Neurology research offices. All computers are password protected and encrypted to further ensure safety.

7.7. Data

The time frame for data analysis will be at the time point when 50% of subjects have been recruited. AE data analysis will be performed every 6 months. Plans for unexpected problems involving risk to participants or others will consist in notification of the principal investigator in order to activate appropriate medical or professional intervention as needed.

7.8. Efficacy

Given the pilot nature of this study, two feasibility outcomes will be included: Consent rate and treatment completion rate. Only four patients are sufficient to calculate a 90% exact binomial confidence interval of (.56, 1) if all four are observed to complete treatment. Thus, this sample size would be large enough to potentially exclude completion rates of 56% or lower. The collection of pilot data from this study will provide initial estimates of the variability and the effect sizes. This information will then be used for the more formal calculations of power and sample size necessary to conduct a future trial.

7.10. Feedback Mechanism

Evaluation and response to any subject complaints will be reviewed by the DSMB. The IRB will be notified of protocols violations and emergence of unexpected AEs at any time during the study. In addition, a report by the DSMB will be provided to the IRB at the end of the study.

Table 1. Schedule of Study Procedures.

Period	**Screen**	**Treatment Period 1**			**Assessment 1[ab]**	**Treatment Period 2**			**Assessment 2[b]**
Visit	-1	1	2-9	10	11	12	13-20	21	22
Visit window	-3 months	-3 months	+1 month	+1 month	±1 month	-3 months	+1 month	+1 month	±1 month
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Medical History	X								
MRI Safety Screening	X					X			
Language Battery	X[j]			X[fh]	X	X[i]		X[fh]	X
Training Tasks		X	X	X	X	X	X	X	X
fMRI[c]		X[g]		X[h]		X[i]		X[h]	
MEG		X[g]		X[h]		X[i]		X[h]	
Randomization		X							
tDCS		X	X	X		X	X	X	
Phone Follow Up/					X				

Visit Reminder[d]									
Adverse Events[d]		X	X	X	X	X	X	X	X
TMS Neuronavigation (for stimulation planning)[e]	X[j]								

[a] Assessment 1, Visit 11 occurs in the middle of the 16-week washout period.
[b] In the case of early termination, Assessment Visit procedures will be performed.
[c] Subjects will undergo mock scanner training. If a subject has been previously engaged in MRI as part of research, the subject may be excused from mock scanner training.
[d] Phone Follow-Ups will be conducted during the 16-week washout period. They will be conducted 4 weeks post Treatment Period 1, 1 week prior to Assessment Visit 1, and 1 week prior to Treatment Period 2. AE review will be completed, and reminders for upcoming visits provided.
[e] TMS Neuronavigation will occur at the investigators discretion.
[f] Language assessment sessions will be conducted after Treatment periods 1 and 2 (visit 10 for period 1 and visit 21 for period 2).
[g] These procedures can occur on 2 or more separate days, but within 3 months before the first treatment session of Treatment Period 1. They may overlap with Visit -1 procedures.
[h] These procedures can occur on 2 or more separate days, but within 1 month after the last treatment session of Treatment Period 1 or the last treatment session of Treatment Period 2.
[i] These procedures can occur on 2 or more separate days, but within 3 months before the first treatment session of Treatment Period 2.
[j] These procedures will take place after Informed Consent is signed, but can occur on 2 or more days prior to first treatment visit. They may overlap with Visit 1 procedures.

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