Application for Review of Human Research: IRB Protocol Summary

Biomedical Research **Section II**

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PROTOCOL TITLE

1. Full Title

Transcranial Direct Current Stimulation for Primary Progressive Aphasia

2. Brief Title

tDCS for Primary Progressive Aphasia

STUDY SPONSORSHIP

1. Funding Sponsor

Funding for this project will come from a grant under Dr. Murray Grossman, number 602943, for the investigation of transcranial direct current stimulation for primary progressive aphasia.

2. Primary Sponsor

H. Branch Coslett

PROTOCOL ABSTRACT

The purpose of this study is to treat the language impairment of subjects with Primary Progressive Aphasia using transcranial direct current stimulation (tDCS) and high definition transcranial direct current stimulation (HD-tDCS). PPA is a slowly progressive impairment in language that may be observed in patients with neurodegenerative conditions such as Fronto-temporal dementia or, less commonly, Alzheimer's Disease. tDCS is a form of non-invasive brain stimulation in which very small current (here,1.5 mA) is applied to the scalp. tDCS will be administered in ten 20 minute sessions over the course of two weeks. Language function will be assessed before, after 1 week of treatment, after 2 weeks of treatment and at 6 and 12 weeks after completion of tDCS. In a sub-study under this protocol, we will pair HD-tDCS with Constraint-Induced Language Therapy (CILT), which preliminary evidence has shown may be a useful speech therapy for individuals with PPA. In this sub-study, we will investigate whether HD-tDCS can enhance the potential benefits of speech therapy (usually very modest in PPA).

OBJECTIVES

1.1 Overall Objectives of tDCS-Only Study

The major objective of the project is to improve language function in patients with Primary Progressive Aphasia using tDCS.

1.2 HD-tDCS+CILT Sub-study Objectives

The objective of the HD-tDCS+CILT sub-study is to improve language function in patients with Primary Progressive Aphasia using a combination of HD-tDCS and a form of intensive speech therapy called Constraint-Induced Language Therapy. The HD-tDCS+CILT sub-study shares many of the design features of the tDCS-Only study in 1.1, therefore, we will include additional information about HD-tDCS+CILT in its own section where relevant to help delineate the differences between these two studies. Any sections that do not include a HD-tDCS+CILT sub-section apply identically to both studies.

1.3 tDCS for svPPA Sub-study Objectives

The objective of the tDCS with svPPA sub-study is to improve language function in patients with semantic variant Primary Progressive Aphasia using a combination of tDCS and speech therapy.

2. Primary Outcome Variable(s)

Outcomes will be assessed with a variety of measures of language including naming and picture description. We will contrast performance before and after tDCS using customary statistical techniques (e.g., ANOVA, t-test, etc). We will also perform analyses of MRI data from participants to determine if there is a correlation between measures such as blood flow and atrophy and improvement from tDCS.

BACKGROUND

In approximately 2000, Nitsche & Paulus demonstrated that weak direct currents applied to the skull could influence brain function. Although still at a relatively early stage of development, the technique has been demonstrated to influence cognition and behavior in more than 300 studies. Importantly, as demonstrated by work in our lab (Kessler, Turkeltaub, Benson, & Hamilton, 2012) ,as well as other sites around the world, the technique has proven to be quite safe. To date, no major adverse effects have been reported with tDCS. We recently reported that 4 weeks of daily tDCS delivered to young normal subjects was well-tolerated with no adverse effects observed (Richmond, Wolk,

Coslett, Vyas, & Olson, 2013). tDCS has been used in the treatment of patients with neurodegenerative diseases (e.g., Benninger et al., 2010; Boggio et al., 2012; Hansen, 2012). We are aware of only one report in which tDCS was administered to a subject with PPA; there was significant improvement in some language functions in the absence of adverse effects (Wang, Wu, Chen, Yuan, & Zhang, 2013). HD-tDCS is an emerging technique of noninvasive brain stimulation that has been tested in a limited number of aphasic populations with comparable effects to traditional tDCS (Sebastian, Tsapkini & Tippett, 2016; Richardson et al., 2015). This new type of stimulation will provide a more focal flow of current than traditional tDCS. Primary progressive aphasia (PPA) is a behavioral disturbance characterized by the insidious onset and slow progression of language impairments in the context of a neurodegenerative disease. In different patients, the deficits may differentially impact comprehension, semantics or verbal fluency. Autopsy studies demonstrate that most patients with PPA suffer from Fronto-temporal dementia but Alzheimer's Disease, Dementia with Lewy Bodies and cortico-basal ganglionic degeneration may also cause the disorder. The disorder leads to a profound impairment in language and, ultimately, to a generalized severe dementia involving all domains of cognition. CILT is an intensive language therapy protocol, first developed by Pulvermuller and colleagues (2001) for use in language rehabilitation following stroke. The central principles of CILT are massed practice over many hours, combined with restricting communication to use of verbal language only (i.e., no gestures or other communication). Throughout the course of a CILT treatment, the difficulty of each stage of therapy is also scaled to individual patient performance, such that patients' language abilities can be sequentially behaviorally "shaped" to ensure a low rate of failure and a gradual increase of difficulty as improvements are made and new skills are retained. Traditional speech therapies are not typically as beneficial for individuals with PPA relative to individuals with post-stroke aphasia due to the progressive nature of the disorder. However, because the central principles of CILT involve massed practice over many hours, paired with constraining communication to the use of language, CILT may thus be useful in the *retention* of language in PPA in addition to aiding in the reacquisition of language after stroke. A recent study has shown modest benefits of an intensive CILT protocol in two individuals with PPA (Hameister et al., 2016), but further questions remain regarding how effective CILT may be for PPA and how long patients can expect the benefits of CILT to last.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Adult subjects between the ages of 45 and 80 with a diagnosis of Primary Progressive Aphasia.

PPA is caused by a neurodegenerative disease. Because these disorders are exceedingly rare under the age of 45 we will not include subjects less than 45 years of age because of uncertainty regarding the diagnosis. As PPA is a rare disorder and we hope to maximize our sample size, all subjects with this diagnosis will be invited to participate.

1.1 Target Population for svPPA sub-study

Adult subjects between the ages of 45 and 80 with a diagnosis of semantic variant Primary Progressive Aphasia.

2. Accrual

There is no information on the basis of which to determine the appropriate sample size. All subjects with Primary Progressive Aphasia who meet Inclusion and Exclusion criteria will be invited to participate.

3. Key Inclusion Criteria for tDCS-Only Study

Study subjects must meet all of the following inclusion criteria: 1. Presence of aphasia attributable to Primary Progressive Aphasia, 2. Between the ages of 45 and 80, 3. Must be able to understand the nature of the study, and give informed consent.

3.1 Key Inclusion Criteria for HD-tDCS+CILT sub-study

Study subjects must meet all of the following inclusion criteria: 1. Presence of aphasia attributable to Primary Progressive Aphasia, 2. Between the ages of 45 and 80, 3. Must be able to understand the nature of the study, and give informed consent. 4. Picture-naming performance at study screening must be at least 50% accurate in the easiest category of screening images (High Frequency Objects)

3.2 Key Inclusion Criteria for tDCS for svPPA

Study subjects must meet all of the following inclusion criteria: 1. Presence of aphasia attributable to the semantic variant of Primary Progressive Aphasia. 2. Between the ages of 45 and 80. 3. Must be able to understand the nature of the study, and give informed consent.

4.1 Key Exclusion Criteria for tDCS-Only and HD-tDCS+CILT

1. Cognitive impairment of sufficient severity to preclude giving informed consent (MMSE < 15).
2. History of seizures or unexplained loss of consciousness; tDCS and HD-tDCS are not associated with seizures but as little information is available we exclude subjects with seizures or unexplained loss of consciousness

3. Pregnancy. There is no evidence of adverse effects from tDCS or HD-tDCS on the fetus but as the question has not been well-studied, we exclude subjects who are pregnant. All women of child-bearing age (that is, still menstruating) will be required to have a negative urine pregnancy test prior to receiving tDCS or HD-tDCS.
4. Subjects with metallic objects in the face or head other than dental apparatus such as braces, fillings, and implants.
5. Subjects with Pacemakers or ICDs.
6. Subjects with previous craniotomy or any breach in the skull; skull defect could be associated with shunting of current leading to unpredictable location and level of current affecting the brain.
7. Subjects with a history of stroke
8. Subjects with a history of small vessel disease

4.2 Key Exclusion Criteria for tDCS with svPPA

Exclusionary criteria for the tDCS with svPPA sub-study include all the criteria listed above, but also include:
1. Usage of sedating medications

5. Vulnerable Populations

Pregnant women, fetuses, neonates or prisoners are not included in this research study; children 18 and older can participate.

6. Populations vulnerable to undue influence or coercion

Special Considerations for Aphasic Patients: Because this protocol involves the enrollment of subjects who are known to have language deficits, some subjects will have difficulty understanding what has been explained to them about the protocol, either verbally or in writing. In other cases, subjects with relatively mild deficits or deficits restricted to the domain of language production will be able to understand what has been explained to them quite readily. For subjects about whom there is uncertainty regarding the comprehension of the ICF and nature of the proposed investigation, we will require that informed consent be obtained from both the patient and a legally authorized representative. The Informed Consent Form (ICF) will be provided to the subject (and to their legally authorized representative when needed) and will be reviewed in detail by the PI or another designated member of the research team. After reading and verbally reviewing the document, the subject (and their representative, as needed) will be asked if there are any questions

or concerns. If the subject (and their representative, as needed) indicates agreement with the participation by signing the ICF, indicate that there are no additional questions, and meet inclusion/exclusion criteria, the subject will be included in the study. In the event that subjects have intact language comprehension and do not require a legally authorized representative, we will document on the consent form that a co-signature by such an individual is not needed by writing "Not applicable" or "N/A" on the signature line of the legally authorized representative. Students will not be enrolled as the disease occurs relatively late in life (50s would be the earliest). The condition is not consistent with employment so subjects will not be Penn employees. The compensation is very modest ($25/hour); we believe that it is very unlikely that this modest compensation alone would be sufficient to induce a potential subject to participate.

7. Subject Recruitment

Patients with Primary Progressive Aphasia will be recruited from two sources: 1) the clinical practices of Drs. Coslett, Hamilton, and Grossman at the Hospital of the University of Pennsylvania, 2) patients participating in Dr. Grossman's project entitled "Neural Basis for Frontotemporal Degeneration" (IRB #298201). Potential patients identified in the clinical practices of the investigators will be contacted directly by the relevant physician. Patients recruited from Dr. Grossman's on-going research project will be contacted by the trained research staff with whom they are currently interacting. We also will use the attached flyers to recruit patients around the University of Pennsylvania campus and Hospital of the University of Pennsylvania grounds, as well as on online FTD/PPA support groups and in-person support groups around the Philadelphia area. Finally, we will sometimes send an email script with information about the study to participants who express an interest in learning more about the research study. Because this is a study of aphasia, a language disorder, oftentimes it is easier for participants to understand information if it is written down and they have time in advance to look things over. This email script will in no way replace the consent form or the consenting process, but we have found these scripts helpful in other studies.

8. Real time safety monitoring

Subjects and equipment will be monitored at all times during tDCS and HD-tDCS studies by a trained member of the research personnel list approved to be on the protocol. During the first stimulation session, participants will come to the lab here at the University of Pennsylvania and a physician will be on call within 5 minutes of the testing room. As long as the subject does not experience any adverse events during that first stimulation session and the research staff have no

reservations, then in all subsequent stimulation sessions, whether conducted in the patient's home or in the laboratory here at the University of Pennsylvania, one of the physicians associated with the study will respond to any concerns within 24 hours. Additionally, the trained personnel administering stimulation will look for any evidence of discomfort in the participant and will verbally inquire about any discomfort. The investigator or trained personnel will also observe and monitor the equipment. In the unlikely event that either the subject or the person administering tDCS or HD-tDCS has significant concerns and the PI cannot be immediately contacted, the subject would be escorted to the Emergency Room.

STUDY DESIGN

1. Phase

Not applicable

2.1 Design of tDCS-Only Study

This is a sham-controlled, full cross-over study design. All subjects with PPA will participate in ten 20minute tDCS stimulation sessions over the course of 2 weeks using 1.5 mA current. A battery of language tasks will be administered before stimulation sessions, after the 10 sessions, and again at 6 and 12 weeks after the stimulation sessions. The 12-week follow up session will serve as the "baseline" session for the following stimulation sessions. All subjects will also participate in ten 20-minute sham stimulation sessions over the course of 2 weeks. During sham tDCS, a 1.5 mA current will be delivered for approximately 30 seconds at the beginning of the sham session before being extinguished over the course of seconds. Participants will be randomly assigned to receive sham or tDCS stimulation first.

For example, a subject who is assigned to sham stimulation sessions first will first undergo baseline language testing. Then the subject will participate in ten 20-minute sham stimulation sessions over the course of 2 weeks. The subject will go through follow up language testing after the 10th sham stimulation sessions as well as 6 and 12 weeks following the sham stimulation sessions. The 12 week follow up session will serve as the "baseline" for the tDCS stimulation sessions, after which the subject will participate in ten 20-minute tDCS stimulation sessions over the course of 2 weeks, using 1.5 mA current.

2.2 Design for* HD-*tDCS+CILT Sub-study

For the HD-tDCS+CILT study, we will use the same sham-controlled, full cross-over design described above, with two exceptions: 1) We will conduct two baseline testing sessions on separate days prior to the start of the 10-day tDCS block, to facilitate screening for CILT and to ensure a stable estimate of language performance at baseline; 2) After the completion of the final 12-week follow-up visit, participants will have the option to undergo an additional 10-day round of "booster" HD-tDCS/sham+CILT. This booster will be open to any patients as an optional incentive for patients whose completion of the study coincided with perceived benefits from the combined therapy. The booster will involve the same time-course of language assessments, HD-tDCS+CILT sessions, and follow-up testing out to 12 weeks after the final HD-tDCS session. This optional third arm of the protocol will thus be identical to the real HD-tDCS arm in all ways (i.e., assessment schedule, subject compensation, tDCS parameters etc.) except that participants may opt in or out as they see fit. In other words, all participants are expected to complete the first two arms of HD-tDCS/sham stimulation; then, those who have completed all the scheduled study visits may choose to undergo a third round, during which we will continue to collect the same data that we have collected throughout the rest of the study.

2.2 Design for tDCS with svPPA *Sub-study*

For the tDCS with svPPA sub-study, we will also conduct a sham-controlled, full cross-over design. Participants will undergo a battery of cognitive and language testing before treatment. Participants will be pseudo-randomly assigned to two groups, A & B. Group A will receive sham stimulation first, while group B will receive active stimulation first. Groups will be stratified by severity of global cognitive impairment as indexed by performance on the Montreal Cognitive Assessment.

All subjects will participate in ten 20 minute tDCS stimulation sessions over the course of 2 weeks using 2 mA current. The battery of tasks will be administered before stimulation sessions, after the 10 sessions, and again at 12 weeks after the stimulation sessions. The 12-week follow up session will serve as the "baseline" session for the following stimulation sessions. All subjects will also participate in ten 20-minute sham stimulation sessions over the course of 2 weeks. During sham tDCS, a 2 mA current will be delivered for approximately 30 seconds at the beginning of the sham session before being extinguished over the course of seconds. Participants will be randomly assigned to receive sham or tDCS stimulation first. After the second treatment/sham period, the cognitive/language tasks will be administered again, and then additionally at 6 and 12 week follow-up sessions.

3.1 Study Duration of tDCS-Only Study

We expect this project to last for approximately 2 years. We expect to enroll approximately 10 subjects annually. Duration of subjects' participation in the study will be approximately 8-10 months.

3.2 Study Duration of HD-*tDCS+CILT Sub-study*

We expect this project to last for approximately 2 years. We expect to enroll approximately 10 subjects annually. Duration of subjects' participation in the study will be approximately 8-16 months, depending on the participants' choice to undergo booster therapy or not.

DRUGS OR DEVICES

We will be using commercially available tDCS and HD-tDCS devices manufactured by Magstim, the Magstim Eldith 1 Channel DC Stimulator Plus. The unit is powered by rechargeable batteries and includes a microprocessor controlled unipolar and bipolar constant source for anodal and cathodal stimulation. We note that this apparatus is currently being employed in an IRB approved protocol (#809185) in which more than 200 tDCS sessions have been conducted without significant adverse effects. The unit is not FDA approved for any clinical purposes. The tDCS unit will be used in a locked laboratory in HUP in which the lab's TMS apparatus is currently situated. Only the PI and other members of his research team have keys to this laboratory. When not in use, the unit will be enclosed in a special, dedicated storage container that will be marked with a statement that the enclosed unit is not to be used for clinical purposes. During these times the unit will be housed in the PIs personal space located in the University of Pennsylvania School of Medicine and stored in a locked cabinet to which only the PI and his staff have access. Additionally, the unit itself will be clearly marked with a statement indicating that it is an investigational instrument only.

STUDY PROCEDURES

1.1 Procedures for tDCS-Only Study

After obtaining informed consent, a baseline language assessment will be performed for all subjects, regardless of whether they will be assigned to sham or real tDCS stimulation first. Depending on the subject, this assessment is expected to take 1-2 hours. Performance will be audio-recorded. The assessment will include the following measures: - Confrontation Naming: we will administer the Boston Naming Test, a commonly used measure of picture naming/word retrieval in which a line drawing is presented and subjects are asked to name the object. - Pyramid and Palm trees: a well-standardized test in which subjects see 3 pictures or words on a page and are asked which two "go together"; for example on one page, the pictures include a drawing of a glove, hand and foot. -Grammatical Comprehension (L-TROG): a standardized test in which subjects are asked to judge whether an auditorily presented sentence is correct. - Category fluency: a series of tasks in which subjects are asked to generate as many words as possible in one minute that are

members of a specific category; semantic categories will include tools, animals, and vegetables. Subjects will also be asked to generate words starting with the letters F, A and S. - Repetition, Reading and Writing (single words) will be assessed using the materials developed by the NACC-FTD consortium; subjects are asked to read, write and repeat a series of words controlled for variables known to influence performance such as length, part of speech (noun, verb), imageability (desk vs. fate), age of acquisition, etc. - Elicited Speech Production: Speech samples will be elicited from subjects by presenting a picture book (e.g., Frog story) or scene to be described (Cookie Theft picture from the Boston Diagnostic Aphasia Examination) and asking subjects to describe what they see. Speech production will be scored off-line with respect to fluency (words/minute), grammatically well-formed sentences, mean length of utterance, nouns/100 words, verbs/100 words, phonemic errors, and phonetic errors. Half of subjects will undergo 10 sessions of sham stimulation first and will then undergo 10 sessions of real tDCS stimulation. Half of subjects will undergo 10 sessions of real tDCS stimulation first and will then undergo 10 sessions of sham stimulation. A complete language assessment will be performed before stimulation sessions, after the 10th stimulation session, and 6 and 12 weeks (± 1 week) after the completion of stimulation sessions. Real tDCS stimulation will be administered using our standard apparatus (Magstim Eldith with 5x5 cm electrodes) using a current of 1.5 mA. (As a frame of reference, we routinely use 2 mA current in other studies.) The anode will be placed over the left fronto-temporal region of the brain and the cathode over the left occipito-parietal region. During sham stimulation, a 1.5 mA current will be delivered for approximately 10 seconds at the beginning of the sham condition before being extinguished over the course of seconds. As there is some evidence that engaging in the activity that one wishes to enhance while undergoing tDCS improves outcome, all subjects will be shown a children's picture book (e.g., the illustrated version of Cinderella) during the 20 minute period of stimulation and asked to narrate the story, regardless of whether they are in real tDCS stimulation or sham stimulation. Participants assigned to receive sham treatment first will cross over to real tDCS treatment after the 12-week follow up session. Each participant will then receive real tDCS stimulation for 10 sessions over the course of two weeks. The stimulation parameters and testing during treatment will be identical to the previous stimulation sessions, except this time participants will receive real tDCS stimulation instead of sham stimulation. Participants assigned to receive real tDCS stimulation first will cross over to sham stimulation after the 12-week follow up session. Each participant will then receive sham stimulation for 10 sessions over the course of two weeks. The stimulation parameters and language testing during treatment will be identical to the previous stimulation sessions, except this time participants will receive sham stimulation instead of real tDCS

stimulation.

Safety and tolerability of the treatment will be assessed in several manners. First, the inclusion/exclusion screening form will be administered both at the initial intake session, as well as at the first session of each 2-week stimulation block. Second, subjects will be queried about new symptoms or adverse effects prior to stimulation on all days when stimulation will be given; should subjects have any concerns, tDCS will not be performed and language will be assessed with fluency tests, naming and a speech sample will be elicited. Third, in the absence of symptoms, language will be assessed at the end of one week of treatment with picture naming, fluency measures and a speech sample will be elicited. Should performance be significantly worse than prior to initiation of treatment, the study will be discontinued; in this event, subjects will be followed on a weekly basis for 4 weeks or until performance returns to baseline (whichever comes first). We propose to use a "significant" change in performance as a cut-off because performance in this condition in the absence of any intervention is quite variable.

1.2 Procedures for HD-*tDCS+CILT Sub-study*

After obtaining informed consent, a baseline language assessment will be performed twice, on separate days, for all subjects, regardless of whether they will be assigned to sham or real HD-tDCS stimulation first. The assessment will include some of the previously listed tests, LTROG, Pyramids & Palm Trees, Word Reading, Sentence Writing, and Sentence Repetition. The Western Aphasia Battery will also be administered. The *Western Aphasia Battery* (WAB: Shewan & Kertesz, 1980) samples a number of different language functions and generates a summary score between 0-100 (Aphasia Quotient, AQ), interpretable as general aphasia severity. They will also be given a 60-item screening/probe image set with 4 categories of picture-naming difficulty. There are, from easiest to most difficult: 1) High Frequency Objects, 2) Low Frequency Objects, 3) High Frequency Actions, and 4) Low Frequency Actions. Participants must perform at a rate of at least 50% picture-naming accuracy in the easiest category (High Frequency Objects) at *both* baseline assessments in order to be enrolled in the study. This is because we will start the therapy at the easiest category where we observed 50% accuracy in naming performance; if participants do not reach this level of accuracy in the easiest category of images, they may be too impaired to participate in the therapy without the therapy itself eliciting undue frustration, fatigue, etc. Subjects will also receive the Communicative Activity Log (CAL; Pulvermuller et al., 2001), which assesses the degree to which patients engage in spontaneous communicative behaviors in their day-to-day life. The items will

address speech output and language comprehension. We will also administer a pen-and-paper version of the CAL to participants' primary caregiver (spouse or family member as relevant) at each time-point. Subjects will undergo this combination of assessments on 9 different study visits, as outlined in the study schedule below. This total of nine assessment visits involves two additional assessment visits compared to the tDCS only (i.e., no therapy) study, due to the addition of two, separate, pre-tDCS baseline assessments.

Visits 1 and 2	**Visit 3**	**Visits 4-11**	**Visit 12**		**Visit 13**	
Baseline language testing and screening	Baseline language testing; Begin HD-tDCS+CILT	HD-tDCS+CILT	HD-tDCS+CILT; Post-HD-tDCS language testing	**(6 week break)**	Post-HD-tDCS language testing	**(6 week break)**

Visit 14	**Visits 15-22**	**Visit 23**		**Visit 24**		**Visit 25**
Post-HD-tDCS/2nd baseline language testing; Begin HD-tDCS+CILT	HD-tDCS+CILT	HD-tDCS+CILT; Post-tDCS language testing	**(6 week break)**	Post-HD-tDCS language testing	**(6 week break)**	Post- HD-tDCS language testing

The HD-tDCS stimulation parameters will be similar to the tDCS-only study. 0.5 cm^2 cup electrodes filled with conductive gel will be placed so that the one electrode (anode) is placed over the targeted region of cortex and electrodes of opposite polarity (cathode) are arranged in four equidistant points around the anode to form an imaginary square. Stimulation will not exceed 1.5 mA in intensity and will not exceed 20 minutes in duration per session. As above, 30-second ramp-up and ramp down periods will be employed before and after stimulation for both real and sham sessions. Afterward CILT, the tDCS electrodes and elastic band or cap will be removed and the subjects' head will be wiped clean. PPA is typically associated with cortical atrophy in the left hemisphere, but the exact location depends on the variant of the disorder. Patients with semantic-variant PPA tend to have atrophy concentrated in the left temporal lobe, whereas patients with nonfluent forms of the disorder tend to have atrophy more concentrated in the left frontal lobe. We will use Soterix tDCS-Explore™ (Soterix Medical Inc., New York, NY) modeling software to place the anode and the cathode over regions that best concentrate the delivery of current to the relevant portion of the left hemisphere. Similar modeling software will be used to determine the exact location of stimulation during HD-tDCS. Based on modeling studies, the current flow during HD-tDCS stays focal, instead of diffusing widely throughout the brain. Exact electrode placement for scalp electrodes presents no additional safety concerns relative to our previous placement of electrodes.

Half of subjects will undergo 10 sessions of sham stimulation first and will then undergo 10 sessions of real tDCS stimulation. Half of subjects will undergo 10 sessions of real tDCS stimulation first and will then undergo 10 sessions of sham stimulation. A complete language assessment will be performed before stimulation sessions, after the 10th stimulation session, and 6 and 12 weeks (± 1 week) after the completion of stimulation sessions.

For each HD-tDCS+CILT session, participants will be set up for HD-tDCS (or sham) administration as described above. We will begin stimulation, and once we ensure the participant is comfortable we will begin the CILT session as soon after the start of stimulation as possible. During CILT, the participant will sit at a table across from the researcher. Both the participant and the researcher will have identical sets of cards. The participant will be required to use language to request a card from the researcher to match a card in their set. The participant must describe the content of the card, using only language, to a level of detail that matches a pre-established difficulty criterion for requesting each card. The researcher will give an example of the desired request at the start of each stage of difficulty. The difficulty of the required request will be scaled to individual participants' skill level depending on performance at screening, and on improvement over the course of the study. For example, if a participant's screening indicates they should begin at the level of basic picture-naming, then at first, participants may ask for a card using one word only (e.g., "elephant"). Contingent on performance, the participant will be asked to make more complex requests (e.g., "Do you have elephant?"). Some participants may start at this level, while participants who are less impaired at baseline may start out at a more advanced level. The goal of the therapy for all participants will be to advance in difficulty level over the course of the treatment; for participants of different abilities, the end points of treatment may be different (e.g., some participants may advance to sentence-level requests, while others may only achieve basic phrase-level requests). To avoid fatigue and frustration, the difficulty of the objects on the cards will also be scaled during real-time participant performance. Correct performance on 8/10 items will result in a difficulty increase within each HD-tDCS+CILT session (e.g., increasing the complexity of the request from "elephant" to "do you have elephant?"). If the participant cannot provide a spontaneous object name, they will be provided a hierarchical series of cues for each object to assist naming. They will be given first a semantic cue (e.g., "it's an animal"), then a phonetic cue (e.g., "the first sound is EL"), then a repetition cue (e.g., "elephant" [participant repeats]). Incorrect performance on 5/10 items will result in a difficulty decrease within the session. If participants progress to the maximum difficulty level for a given category of stimuli (i.e., sentence-level requests), the stimuli used at the next HD-

tDCS+CILT session will be from a more difficult category (e.g., moving from high to low frequency objects, or from low frequency objects to high frequency actions, and so on). Sessions will be audio-recorded and performance will be scored across cuing levels. The CILT sessions will last up to 1.5 hours each, with HD-tDCS terminating after 20 minutes of stimulation.

Safety and tolerability of the treatment will be assessed in several manners. First, the inclusion/exclusion screening form will be administered both at the initial intake session, as well as at the first session of each 2-week stimulation block. Second, subjects will be queried about new symptoms or adverse effects prior to stimulation on all days when stimulation will be given; should subjects have any concerns, HD-tDCS will not be performed and language will be assessed with fluency tests, naming and a speech sample will be elicited. Third, language will be assessed immediately following the 10th HD-tDCS+CILT session with the WAB, the 60-item image set, and the patient/caregiver CAL. Should there be a clinically significant decrease in performance on the WAB (a reduction in score of 5 or more points) compared to the participant's WAB score on day 1 of the treatment, the participant's visits will be discontinued; in this event, subjects will be followed on a weekly basis for 4 weeks or until performance returns to baseline (whichever comes first). We propose to use a "significant" change in performance as a cut-off because performance in this condition in the absence of any intervention is quite variable.

After the final visit of the HD-tDCS+CILT sub-study (i.e., the last 12-week follow-up), participants will have the option to participate in one additional round of 10 HD-tDCS+CILT sessions, to be scheduled no earlier than 3 months after study completion and no later than 6 months following study completion.

1.3 Procedures for tDCSwith svPPA Sub-Study

After obtaining informed consent, a baseline language assessment will be performed twice, on separate days, for all subjects, regardless of whether they will be assigned to sham or real tDCS stimulation first. Depending on the subject, this assessment is expected to take 1-2 hours. Performance will be audio-recorded. The assessment will include the following measures:

- Global Cognition: we will administer the Montreal Cognitive Assessment, a commonly used measure of cognitive abilities.
- –Semantic Memory: Pyramid and Palm trees: a well-standardized test in which subjects see 3 pictures or words on a page and are asked which two "go together"; for example on one

page, the pictures include a drawing of a glove, hand and foot.

- -Category fluency: a series of tasks in which subjects are asked to generate as many words as possible in one minute that are members of a specific category; semantic categories will include tools, animals, and vegetables.
- –Executive Processing: The Digit Symbol task from the Wechsler Adult Intelligence scale will be administered to test sustained attention and executive ability. Subjects will also be asked to generate words starting with the letters F, A and S.
- Naming: The Peabody Picture Vocabulary Test (PPVT-IV) and the Philadelphia Naming Test (PNT) will be administered, both commonly used tests to assess naming and general language ability.

Half of subjects will undergo 10 sessions of sham stimulation first and will then undergo 10 sessions of real tDCS stimulation. Half of subjects will undergo 10 sessions of real tDCS stimulation first and will then undergo 10 sessions of sham stimulation. A complete language assessment will be performed before stimulation sessions, after the 10th stimulation session, and 12 weeks and 6 months (± 1 week) after the completion of stimulation sessions. Real tDCS stimulation will be administered using the Soterix 1x1 using a current of 2 mA. The cathodal current will be split across two electrodes ($5cm^2$) positioned over the left and right temporal regions respectively. The anodal electrode (5x7cm) will be placed over the forehead. During sham stimulation, a 2 mA current will be delivered for approximately 10 seconds at the beginning of the sham condition before being extinguished over the course of seconds. After the first 10 minutes of stimulation, in both real and sham conditions, participants will begin the behavioral treatment, which will continue for 45 minutes; therefore there will be 20 minutes of concurrent tDCS and behavioral therapy.

Prior to initiating treatment, we will craft an individualized training lexicon for each patient. This training vocabulary contains familiar people, household items, foods, activities, cloths, and hygiene implements. Target words are represented by photographs of the patient's own items. We will employ several item-level controls to examine treatment generalization. The first will test the impact of personal familiarity by asking patients to name and generate features for canonical rather than personal photographs. The second condition will evaluate within-category generalization by asking patients to name and generate features for their own untrained items. The final item-level comparison will examine generalization of naming accuracy to untrained

exemplars from the Philadelphia Naming Test. Once an item pool is established, baseline naming accuracy and eye-tracking measures will be acquired. During baseline testing sessions, we will identify target items as either known or vulnerable based on their consistency of being named. We will isolate vulnerable versus mastered items for each patient and apply different training for each. Vulnerable items will be treated using a modified semantic feature analysis approach. Mastered items will be trained using cued picture naming. Assignment of a particular target item to either treatment condition is dynamic. Once a vulnerable target item has been mastered, it will move to the mastery list. Similarly, mastered items later forgotten can move to the vulnerable list. Each treatment session will include pretest/post-test naming probes for vulnerable items. Mastery item lists will be probed once weekly.

Following the pretest, a clinician will train all of a patient's vulnerable target items in completely randomized order. Training proceeds by positioning the target photograph in the center of a blank feature matrix. The clinician then announces the target item's semantic features. After this modeling procedure, the clinician cues the patient to name the target picture, generate its features, and name it again. The same item will be present repeatedly until the patient can successfully generate the target image's name and >50% of its features. The clinician will then proceed to the next item, continually cycling through the list for 45 to 60 minutes. In addition to intensive semantic training on vulnerable items, patients will train on naming their mastery items, albeit less frequently and less comprehensively. Mastery list training involves random presentation of the target pictures with cues to name each. No clinician feedback is given, and the final response is scored for accuracy.

Safety and tolerability of the treatment will be assessed in several manners. First, the inclusion/exclusion screening form will be administered both at the initial intake session, as well as at the first session of each 2-week stimulation block. Second, subjects will be queried about new symptoms or adverse effects prior to stimulation on all days when stimulation will be given; should subjects have any concerns, tDCS will not be performed and language will be assessed with fluency tests, naming and a speech sample will be elicited. Third, in the absence of symptoms, language will be assessed at the end of one week of treatment with picture naming, fluency measures and a speech sample will be elicited. Should performance be significantly worse than prior to initiation of treatment, the study will be discontinued; in this event, subjects will be followed

on a weekly basis for 4 weeks or until performance returns to baseline (whichever comes first). We propose to use a "significant" change in performance as a cut-off because performance in this condition in the absence of any intervention is quite variable.

2. Statistical Analysis

Data from each subject will be analyzed using a within-subject design in which change in performance from the baseline testing session to the post-therapy (0, 6, 12 weeks post tDCS) will be compared using t-tests, ANOVAs and other univariate statistics. As it is most relevant to real-world behavior, elicited speech production will serve as the primary endpoint. Depending on our ability to recruit a reasonable sample, group analyses will be also be performed. Finally, we note that high quality imaging will be available for the majority of subjects. Note that we are not proposing to obtain imaging under the auspices of the present study; this data will be available from Dr. Grossman's previously cited protocol. We will perform exploratory analyses in which we attempt to determine if specific imaging parameters (e.g., cortical thickness, degree of atrophy) predict response to tDCS.

3. Confidentiality

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
☐ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.

☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other *(specify):* _____

Subject confidentiality will be maintained by keeping records in a secure location. Most of the information will take the form of computer files; these will be de-identified by using a coding process under which subjects are identified by an assigned subject number and the date of the testing. Subject names, ages and ethnicity will be recorded only in a secure, password protected computer location. Signed consent forms and HIPAA forms will be maintained in a secure file at least until the project is terminated. In tasks assessing language production, subjects' responses will be recorded in a digital fashion for later analysis. The digital files will be destroyed after the experiment is completed. In tasks assessing language production, subjects' responses will be recorded in a digital fashion for later analysis. The digital files will be destroyed after the experiment is completed. In order to determine if a subject should be disqualified by virtue of neurologic or psychiatric issues or is consuming a medication that may alter brain membrane potentials, potential subjects will be asked if they have a history of any of the following: seizures, stroke, episodes of loss of consciousness, or psychiatric illness requiring treatment. They will also be asked to indicate if they

are taking medications for seizures, bipolar disorder, ADHD, OCD, schizophrenia or psychosis. PHI that is to be collected includes subject names, addresses, contact information and Social Security Number. The latter is necessary for subject payment. This information will be stored in a protected computerized subject database. PHI will not be disclosed to anyone not listed in the IRB-approved list of personnel.

4. Subject Privacy/Protected Health Information

The potential subjects for this study will be drawn from the practices of the cognitive neurologists at the Univ. of Penn, 3 of whom are participating in the study (Coslett, Hamilton, Grossman). Our colleagues (Chatterjee, Wolk, Aguirre) know of the study and have indicated that they would be happy to refer appropriate subjects. Potential subjects will be contacted initially by their treating physician; after learning of the study and indicating that they want to hear more about it, they will be contacted by study personnel. There is a chance that subjects will contact us; the world of Primary Progressive Aphasia is pretty small; the disorder is rare and there are support groups and links between patients. It is possible that someone seen at another institution will hear of the study and contact us to see if they are eligible. Assuming they met Inclusion/Exclusion criteria, these subjects would be included in the study. Patients referred from clinicians other than Drs. Grossman, Hamilton or Coslett will be subject to an initial screening visit prior to enrollment to determine eligibility and diagnosis confirmation.

5. Tissue Specimens

Not applicable.

6. Genetic Testing

Not applicable.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

Risks from tDCS in the normal population appear to be minor. The most common adverse effect in a published review of our experience at Penn (Kessler et al., 2012) was itching and mild burning at the site of stimulation (that is, under the electrode). We have not observed significant adverse effects in more than 500 testing sessions and, to the best of our knowledge, no significant adverse effects have been reported elsewhere. Participants receiving sham stimulation can sometimes

experience side effects similar to those experienced during real tDCS stimulation. This is because sham stimulation involves approximately 30 seconds of real stimulation before the machine shuts off. tDCS is currently regarded by the IRB as a minimal risk procedure in normal subjects. tDCS has been employed safely in patients with a variety of neurologic disorders including stroke and degenerative diseases (references cited previously). We are aware of one abstract (Wang et al., 2013) reporting tDCS as a treatment in a single subject with PPA in which the procedure appears to have been well-tolerated and possibly efficacious (the data are very limited). Overall, the potential risks appear to be modest. The risks associated with tDCS are not altered if the stimulation is conducted at a patient's home or if it is conducted in the lab. Similarly, HD-tDCS is safe and equally well-tolerated as conventional tDCS. Consistent with the favorable safety profile of tDCS, protocol #814366 was approved by the IRB of the University of Pennsylvania and HD-tDCS was deemed a minimal risk technique.

2.1 Potential Study Benefits of tDCS-Only Study and tDCS with svPPA sub-study

The study is being performed to determine if tDCS improves subjects' language performance. The potential benefit of the study to the subjects, therefore, is that they will improve with respect to language function. The study will also be of benefit to the community of physicians and clinicians attempting to treat PPA.

2.2 Potential Study Benefits of HD-tDCS+CILT Sub-study

The study is being performed to determine if HD-tDCS in combination with CILT improves subjects' language performance. The potential benefit of the study to the subjects, therefore, is that they will improve with respect to language function. This may occur during CILT+sham, CILT+HD-tDCS, or both. The study will also be of benefit to the community of physicians and clinicians attempting to treat PPA.

3. Alternatives to Participation

The alternative to participation is to not participate. Subjects' participation in other research projects will not be influenced by a decision to not participate in this project.

4. Data and Safety Monitoring

The PI will monitor the progress of the study, including safeguarding data and monitoring for

adverse effects.

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.

Not applicable.

6. Risk/Benefit Assessment

The risks as well as the potential benefit of the study are modest. tDCS has been delivered to subjects with primary degenerative diseases of the brain in multiple studies without adverse effects. The benefits, however, are also expected to be modest. The treatment may improve language function but in the setting of a primary degenerative condition, the benefit is likely to be modest. There is no reason to believe that the treatment will modify the underlying course of the disease.

SUBJECT COMPENSATION

Subjects will be compensated at a rate of $25/hour for their time while participating in the study.

Typically, participants are compensated via mailed check, however, we have received approval from the department to use the GreenPhire clin-card system. The GreenPhire clin-card is a reloadable debit card. These can be used to provide payment for participation in research studies, as well as payment for transportation costs related to participation in research. Each subject is given a GreenPhire card and, once the system is set up, subjects can be paid immediately following each session, including for any transportation costs. Subjects can then use the card like a credit or debit card at various merchants, can withdrawal money at any ATM (though there may be fees associated with this option), or can withdrawal the balance of the card at any bank (no fees associated with this option). This method of payment is only an option and is not a requirement. Participants and the research staff will together make the decision about which payment option is best.

INFORMED CONSENT

1. Consent Process

Consent will be obtained by Drs. Coslett, Grossman or Hamilton or one of their research associates. Subjects who are not judged to be competent to give informed consent by the investigators will have their Legally Authorized Representative (LAR) give consent on their behalf. In these cases,

the LAR will sign the ICF/HIPAA in the appropriately labeled space.

2. Waiver of Authorization

Not applicable.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Research staff related to this project include the PI, Co-investigators (Drs. Hamilton and Grossman) and other personnel. All research staff will undergo training on research practices involving human subjects, including the protection of subject confidentiality, and will maintain current certification in patient oriented research. Moreover, all investigators will have experience administering tDCS. During the first stimulation session, participants will come to the lab here at the University of Pennsylvania and a physician will be on call within 5 minutes of the testing room. As long as the subject does not experience any adverse events during that first stimulation session and the research staff have no reservations, then in all subsequent stimulation sessions, whether conducted in the patient's home or in the laboratory here at the University of Pennsylvania, one of the physicians associated with the study will respond to any concerns within 24 hours. The trained personnel administering stimulation will look for any evidence of discomfort in the participant and will verbally inquire about any discomfort. The investigator or trained personnel will also observe and monitor the equipment. In the unlikely event that either the subject or the person administering tDCS has significant concerns and the PI cannot be immediately contacted, the subject would be escorted to the Emergency Room.

Staff will also be trained on the correct administration of the specific psychometric tests of language and cognition employed in proposed research. Subject Recruitment: Patients with PPA will be recruited from two sources: 1) the clinical practices of Drs. Coslett, Hamilton, and Grossman, 2) Dr. Grossman's IRB-approved protocol entitled "Neural Basis for Frontotemporal Degeneration" (#298201). Potential subjects identified in the clinical practices of Drs. Coslett, Hamilton and Grossman will be contacted by their treating physician. Potential subjects involved in research with Dr. Grossman and his team will be contacted by the research staff with whom they interact in the on-going research project.

Facilities: Subjects will be stimulated and tested in HUP or Perelman School of Medicine buildings. Depending on the availability of rooms, three testing sites may be employed: Neurology out-patient

offices in the Perelman Center, Neurology out-patient offices on Ravdin 2 or the laboratory of Dr. Grossman (Gibson 3). The HD-tDCS apparatus is portable and no special equipment is required. Additionally, if it is convenient for the patient, we may conduct stimulation sessions in the patient's home. In order to be eligible for home visits, patients must live within 40 miles, or approximately one hours, of the University of Pennsylvania. Ultimately, the discretion for eligibility and scheduling will be up to the researcher and the Principal Investigator, in order to best effectively and efficiently manage the lab's resources. If patients do qualify for home visits, they will come to the lab for their first stimulation session. If the patient does not experience any adverse events during that stimulation session and if the other requirements are met, then all subsequent stimulation sessions would be conducted in the patient's home. Again, we would like to stress that this is only an option, not a requirement, which patients may choose if it is more convenient for them. Patient visits not requiring the use of tDCS may be conducted at the patient's home if this situation proves to be more convenient for the patient.

Device: Recently, Magstim, the largest manufacturer of TMS equipment in the world, has developed a tDCS apparatus, the Magstim Eldith 1 Channel DC Stimulator Plus. The unit is powered by rechargeable batteries and includes a microprocessor controlled unipolar and bipolar constant source for anodal and cathodal stimulation. Both tDCS and HD-tDCS will be administered using Magstim Eldith DC stimulators. A Soterix 4x1 HD-tDCS adaptor will be used to convert the traditional tDCS unit to allow for HD stimulation. We note that these apparatuses are currently being employed in an IRB approved protocol (#809185 and #814366) in which more than 200 tDCS sessions have been conducted without significant adverse effects. The unit is not FDA approved for any clinical purposes. The tDCS and HD-tDCS units will be used in a locked laboratory in HUP in which the lab's TMS apparatus is currently situated. Only the PI and other members of his research team have keys to this laboratory. When not in use, the unit will be enclosed in a special, dedicated storage container that will be marked with a statement that the enclosed unit is not to be used for clinical purposes. During these times the unit will be housed in the PIs personal space located in the University of Pennsylvania School of Medicine and stored in a locked cabinet to which only the PI and his staff have access. Additionally, the unit itself will be clearly marked with a statement indicating that it is an investigational instrument only.

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