Study Title: Home-based tDCS in Frontotemporal Dementia or Alzheimer's Disease

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IRB Title: Effects of transcranial direct current stimulation (tDCS) in primary progressive aphasia (PPA)

IRB Approved Protocol

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1. Abstract

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

Primary progressive aphasia (PPA) is a common type of neurodegenerative disease that affects first and foremost language abilities. Mild cognitive impairment (MCI) is slowly progressive decline in a single domain of cognition (e.g. language) not attributable to motor or sensory loss, without impediment of social or occupational function (Petersen & others, 2003). MCI can be an early sign of neurodegenerative disease, or can be due to normal aging. When language is the prominent affected domain in MCI, the person may later meet criteria for PPA or may progress to the clinical syndrome of Alzheimer's dementia (AD). Spelling, naming, and working memory (i.e. repetition) are among the language abilities affected early in the course of PPA, and different variants of PPA have distinct deficits in these domains (Budd et al., 2010; Sepelyak et al., 2011). Naming (word retrieval) and spelling can also be among the earliest functions impaired in MCI when language is the prominent affected domain. A subset of individuals with PPA also present with speech production impairments (dysarthria and apraxia of speech, AOS) (Duffy et al., 2014). Dysarthria is commonly seen in amyotrophic lateral sclerosis (ALS), in which there can be flaccid, spastic, and mixed dysarthria presentations (Tomik & Guiloff, 2010). Speech production impairments can negatively affect functional communication, social independence, and quality of life. Currently, there is no curative treatment for these individuals. Transcranial Direct Current Stimulation (tDCS) is a relatively new, safe, non-invasive, non-painful electrical stimulation of the brain that has resulted in improved language and cognitive abilities in stroke and AD when administered during traditional behavioral (language) therapy (Baker et al., 2010; Boggio et al., 2009; Ferrucci et al., 2008; Floel et al., 2011; Monti et al., 2008; Schlaug et al., 2008). tDCS alters neuropeptide concentrations at the sites of stimulation, which is particularly important because individuals with PPA have a specific neuropeptide signature. It has been shown that anodal tDCS can enhance language and motor performance, visuo-motor learning, and recognition memory or working memory. In this research project, we intend to investigate the behavioral and neuromodulatory effects of tDCS during: 1) spelling therapy in PPA and MCI participants over time and 2) speech therapy in PPA and ALS participants. We hypothesize that anodal tDCS when administered in combination with spelling, naming, working memory, or speech therapy will improve speech and language performance of PPA,MCI, and ALS participants at least in the short term more than behavioral therapy alone and that improvements may generalize to some other cognitive functions and functional communication. Research on the effects of tDCS in sleep and exercise is growing, but the effects are not yet conclusive. In some studies, tDCS has been found to improve sleep in individuals with fibromyalgia, bipolar disorder, and post-polio when premotor or motor areas are stimulated (Acler et al., 2013; Minichino et al., 2014; Roizenblatt et al., 2007), but it was found to depend on the area stimulated, i.e., it decreased sleep efficiency when the dorsolateral pre-frontal cortex was stimulated (Roizenblatt et al., 2007). The use of tDCS is more controversial in studies of exercise; some studies have shown increased post-exercise oxygen uptake with tDCS (Montenegro et al., 2012), while another has found similar perceived exhaustion rates for tDCS and sham (Okano et al., 2015). However, there are other reports that show that behavioral effects of tDCS depend on the task it is coupled with.

In this research project we will investigate whether and how tDCS alters the neuropeptide signature in participants with PPA and MCI. We will use proton magnetic resonance spectroscopy (^{1}H-MRS) to monitor neuropeptide concentrations at the areas of stimulation. We hypothesize that tDCS will stabilize the decline of a specific neuropeptide, but only in those areas of the brain where tDCS effectively resulted in more efficient gains in language compared to language therapy alone (with sham tDCS). We will investigate whether brain-derived neurotrophic factor (BDNF) (i.e., the most common molecule associated with cognitive decline and impaired synaptic transmission in aging and neurodegeneration) is a sex-differentiated molecular determinant and mechanism of language and cognitive decline and treatment in neurodegeneration.

In addition, we will investigate the effects of tDCS during speech therapy for dysarthria in individuals with neurodegenerative diseases (PPA, ALS). The goal of this study is to determine whether tDCS combined with speech therapy can improve speech intelligibility in patients with PPA and ALS. We hypothesize that combined tDCS and speech therapy will result in improved sentence intelligibility, perceptual and acoustic speech characteristics, and functional communication compared to sham tDCS (placebo) and speech therapy.

Furthermore, the study aims to investigate the effects of a tDCS-enhanced novel word learning intervention on vocabulary acquisition across different age groups, specifically comparing healthy younger adults and healthy older adults. By understanding the differential impacts of age and clinical conditions on language learning, this research seeks to illuminate the extent to which challenges in word treatment in clinical populations are attributable to disease processes versus age-related decline.

Study results may help optimize future intervention in individuals with PPA,MCI, and ALS by providing treatment alternatives in neurodegenerative conditions with no proven effective treatment. A better understanding of the therapeutic and neuromodulatory effects of tDCS in PPA,MCI, and ALS will offer insight into ways of impeding neurodegeneration that may improve quality of life for individuals with PPA,MCI, and ALS and may provide insights into the mechanisms of this treatment for augmenting therapy for stroke as well.

Objectives

Primary Objective 1 (cognitive/language intervention): To determine whether behavioral therapy coupled with anodal tDCS will improve the language performance of participants with PPA and MCI more efficiently and for greater duration than behavioral therapy alone (i.e. in the sham condition). tDCS targets will be the supramarginal gyrus (SMG), middle temporal gyrus (MTG), and inferior frontal gyrus (IFG). These areas are critical for both phoneme-grapheme conversion and for access to orthographic representation of words and their meaning in the spelling process (Cloutman et al., 2009). For individuals with naming or working memory/repetition deficits, tDCS targets will also be IFG, MTG, angular gyrus (AG), and SMG, as these are also areas of the brain consistently activated in these tasks (Jarso et al., 2013; Philipose et al., 2007). For individuals with executive functioning deficits, the tDCS target will be the dorsolateral prefrontal cortex (DLPFC) to compare language vs. executive functions after stimulation of the DLPFC. For individuals receiving home-based tDCS and computerized cognitive therapy, tDCS targets will include perisylvian areas and their right hemisphere homologs. For individuals receiving home-based tDCS there will be an optional 3-week cognitive behavioral therapy (CBT) where the tDCS target will be the LDLPFC. Furthermore, to better understand how learning and tDCS effectiveness in the patient groups compares to these effects in healthy aging, we will examine word learning in healthy control participants, who will engage in a novel word learning intervention paired with tDCS.

Hypothesis 1a: Both behavioral therapy and combined tDCS-behavioral therapy will result in improved language performance for trained and untrained stimuli, from baseline to post-treatment; however, goals will be achieved more rapidly with the combined intervention.
Hypothesis 1b: Improvements in language achieved with combined tDCS-behavioral therapy but not behavioral therapy alone will persist at 2 weeks, 2 months, and 6 months post-intervention.
Hypothesis 1c: Stimulation of the proposed areas during behavioral therapy will improve performance in other language and cognitive functions specific to the region of interest. Specifically, for SMG, improvements will be observed in spelling, naming, working memory and repetition; and for IFG and MTG, in spelling, naming, working memory, articulation, and syntactic comprehension.
Hypothesis 1d: The therapeutic effect of tDCS will exhibit an interaction between hemisphere of stimulation (left vs. right) and stage of disease (early vs. middle), such that left hemisphere stimulation will be more effective at an early stage, whereas at later stages right hemisphere stimulation will augment compensation by this hemisphere and will be more effective than left hemisphere stimulation.
Hypothesis 1e. Improvements in language achieved with combined IFG tDCS-behavioral therapy or sham and behavioral therapy alone will correlate with increases in daily physical activity and evening sleep efficiency and quality (using both self-report and objective measures) and there will be greater improvements in sleep efficiency and exercise in the tDCS condition as opposed to sham, because the area we target (left or right IFG) with 2x2 in electrodes incorporates premotor and motor areas that have been found to improve the perceived difficulty and amount of exercise and sleep efficiency.
Hypothesis 1f: Beginning with a 3-week CBT treatment with tDCS over the DLPFC before beginning computerized cognitive/speech therapy at home will foster motivation and engagement in the consequent therapy by establishing routine, form, and helping manage psychological barriers to therapy beforehand.
Hypothesis 1g: The tDCS-enhanced novel word learning intervention will result in improved vocabulary acquisition from baseline to post-treatment; however, healthy younger adult participants will demonstrate greater gains in word learning outcomes compared to healthy older adults, with both groups showing greater improvements than patient groups in standard word learning intervention.

Primary Objective 2 (speech intervention): To determine whether tDCS combined with speech therapy will improve sentence intelligibility [based on the Sentence Intelligibility Test (SIT)] (Yorkston et al., 1996) in participants with neurodegenerative speech impairment compared to speech therapy alone (sham condition). The tDCS targets will be the left precentral gyrus (PrCG) which is an area associated with dysarthria (Wong et al., 2022; You et al., 2010) and left IFG which is an area associated with AOS (Themistocleous et al., 2021).

Secondary Objective 2a: To determine whether tDCS combined with speech therapy will change the duration and acoustic measures of sustained phonation (fundamental frequency, jitter, shimmer, noise-to-harmonics ratio, pitch range/variation, loudness range/variation using PRAAT software), sequenced and alternating motion rates (SMR's, AMR's), conversation/reading rate, and speech articulation accuracy at the word, phrase, sentence, and paragraph level in participants with neurodegenerative speech impairment compared to speech therapy (sham condition).

Secondary Objective 2b: To determine whether tDCS combined with speech therapy will improve scores on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (Cedarbaum et al., 1999). in participants with neurodegenerative speech impairment compared to speech therapy (sham condition).

Secondary Objective 2c: To determine whether tDCS combined with speech therapy will improve scores on the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA-FACS, Fratalli et al., 1995) in participants with neurodegenerative speech impairment compared to speech therapy (sham condition).

Hypothesis 2a-c: We hypothesize that combined tDCS and speech therapy will result in improved sentence intelligibility, perceptual and acoustic speech characteristics, and functional communication compared to sham tDCS (placebo) and speech therapy.

Primary Objective 3 (imaging): To develop biomarkers for the effects of intervention using ^{1}H-MRS. We will use ^{1}H-MRS to detect NAA and GABA before, after and at follow-up intervals and evaluate the correlation between: (1) NAA/ GABA levels and (2) spelling, naming, and/or repetition accuracy of participants with PPA and MCI at each time point.
Hypothesis 2a: We hypothesize that tDCS coupled with behavioral therapy will result in enhanced, relative to behavioral therapy alone (with sham tDCS), levels of NAA at the stimulation sites where tDCS resulted in improved spelling relative to behavioral therapy alone.
Hypothesis 2b: We hypothesize that tDCS coupled with spelling therapy will result in reduced, relative to behavioral therapy alone (with sham tDCS), levels of GABA at the stimulation sites where tDCS resulted in improved language relative to behavioral therapy alone.

Primary Objective 4 (molecular mechanisms)
Part 1: (A) To determine whether BDNF levels in plasma or saliva are related to language and cognitive decline in PPA, differently in men and women (cross-sectionally, before treatment). (B) To evaluate whether tDCS modulates BDNF levels and language and cognitive performance differently in men and women, relative to baseline (before treatment). We will measure BDNF levels, as well as other synaptic proteins (e.g., NPTX2, NRXN2a, AMPA4), language and cognitive performance, before, immediately after and 6 months post-treatment.
Part 2: To measure the correlation between tDCS-induced changes in functional connectivity and BDNF in men and women. We will measure brain and skull anatomical variables from scans, and analyze data from resting state functional magnetic resonance imaging (rsfMRI) before, immediately after, and 6 months post treatment.
Hypotheses: (A) tDCS will induce differential functional connectivity (FC) changes in men and women; (B) these FC changes will correlate with changes in BDNF blood levels; (C) and BDNF changes will correlate with changes in therapy outcomes in men and women, after controlling for potential sex-dependent cranial and neuroanatomical differences. (D) Changes will last for up to 6 months.
Part 3: To identify whether gene mutations (e.g., val66met) that affect BDNF secretion in men and women with PPA predict tDCS effects on BDNF levels, behavioral outcomes and FC network modulations. We will analyze behavioral tDCS effects (over sham) with regard to the interaction between genetic mutation and sex. We will also test whether known mutations that are responsible for Alzheimer's disease pathology e.g., the APOE4 affect tDCS effects, since this genetic mutation can be isolated with the same genetic sequence procedure (Taqman). We will carry out genetic testing at the beginning of treatment and stratify tDCS groups accordingly.

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

During the past few years, a form of electrical stimulation of the brain, transcranial Direct Current Stimulation (tDCS) has been rediscovered and shown to enhance cortical function (Floel et al., 2008; Fritsch et al., 2010; Wassermann & Grafman, 2005) when anodal current is applied in healthy individuals (Floel et al., 2008; Iyer et al., 2005). So far, tDCS has been mainly used to improve motor and language recovery in post-stroke aphasia (Baker et al., 2010; Fiori et al., 2011, p. 201; Floel et al., 2011; Fridriksson et al., 2011; Hamilton et al., 2011; Monti et al., 2008; Schlaug et al., 2008). A few studies have used tDCS in participants with neurodegenerative diseases such as Alzheimer's Disease (AD) (see(Freitas et al., 2011)for a review) and have shown that it improved recognition memory in those participants (Boggio et al., 2009; Ferrucci et al., 2008; Sparing et al., 2008) especially when applied together with behavioral therapy but long-term effects have not been clearly identified yet. In recent years, studies of tDCS in PPA by various groups, including our lab, have demonstrated significant augmentative tDCS effects in several

language functions by stimulating left hemisphere language regions (Cotelli et al., 2014; Fenner et al., 2019; Ficek et al., 2018; Gervits et al., 2016; Hung et al., 2017; Sheppard et al., 2022; Tsapkini et al., 2014; 2018). As research advances there is a growing interest in describing the physiological effects of this therapy (Stagg & Nitsche, 2011) as well as the changes it induces to brain activity (Nitsche et al., 2004). A handful of studies have used fMRI to look at the effects of tDCS in the brain either during or after stimulation (Antal et al., 2011; Jang et al., 2009; Kwon et al., 2008; Polania et al., 2011; Stagg et al., 2009). However, all these studies used healthy individuals or rats (Takano et al., 2011). Furthermore, there are only a few treatment studies in PPA (see (Mesulam, 2007), for a discussion) and these studies have focused on the treatment of word retrieval, primarily in semantic dementia, i.e. the semantic variant of PPA (Graham et al., 1999; Henry et al., 2008; Heredia et al., 2009; Jokel et al., 2006, 2010) with encouraging results of language therapy at least for trained items. Similarly, there are also a few studies of behavioral word retrieval treatment in non-fluent/agrammatic PPA (Jokel et al., 2009; Marcotte & Ansaldo, 2010; McNeil et al., 1995; Schneider et al., 1996) with no evidence of lasting effects, two studies with naming interventions for PPA (Beeson et al., 2011; Newhart et al., 2009) and only two studies with a spelling intervention one of which is from our lab (Rapp & Glucroft, 2009; Tsapkini & Hillis, 2013). To date we are not aware of any published study that has evaluated the effect of spelling, naming, or repetition therapy combined with tDCS in PPA or MCI participants.

Few studies have explored tDCS for the treatment of motor speech impairments. These studies have focused on post-stroke aphasia and AOS (Marangolo et al., 2011; 2013), AOS in PPA (Themistocleous et al., 2021), post-stroke dysarthria (Wong et al., 2022; You et al, 2010), and neurodegenerative cerebellar ataxia (Benussi et al., 2017) and showed improvements in speech production with behavioral therapy combined with tDCS and with tDCS alone.

Neuromodulation in ALS has the potential to slow disease progression in ALS. Benussi et al. (2019) explored concurrent bi-anodal motor cortex and cathodal spinal stimulation (corticospinal tDCS), seeking a synergistic effect. The randomized controlled trial included 30 patients with ALS who received tDCS applied 20 min/day at an intensity of 2 mA for 2 weeks, showing a significant improvement or stabilization in muscle strength, quality of life scores, and caregiver burden. This improvement was associated with the restoration of intracortical connectivity measures, as evaluated by transcranial magnetic stimulation, indirectly assessing $GABA_A$ and glutamatergic-mediated circuits. Subsequently, Benussi et al. (2023) sought to assess the long-term effects of multiple sessions of anodal bilateral motor cortex tDCS and cathodal spinal tDCS in patients with ALS, determine whether two rounds of tDCS treatment are more effective than a single treatment, and explore potential effects on prognostic ALS markers, such as serum neurofilament light chain (NfL). Compared to sham stimulation, cortico-spinal tDCS significantly improved global strength, caregiver burden, and quality of life scores, which correlated with the restoration of intracortical connectivity measures. Serum neurofilament light levels decreased among patients who underwent real tDCS but not in those receiving sham tDCS.

Although we do not know the exact mechanisms by which tDCS works, it has been claimed that the low current applied on the scalp has the potential to alter synaptic excitability at the stimulation area (Nitsche et al., 2004; Stagg & Nitsche, 2011). We therefore hypothesize that effects of generalization to other functions will depend on the area stimulated. In the existing literature effects of tDCS in the areas stimulated have been correlated with the cognitive functions subserved by these areas. Furthermore, it has been shown that stimulation of specific areas affects only functions subserved by these areas but not others; Ferrucci and colleagues (2008) have shown that stimulation of the temporo-parietal junction affected word recognition but not visual attention which was subserved by different areas. There is only one other study that has looked at transfer of treatment effects to other language functions. (Marangolo et al., 2011)) have shown that beneficial effects from syllable production training in combination with stimulation at the left inferior frontal gyrus (IFG) of patients with stroke transferred to other production tasks such as word repetition and reading. In the present study we will test the hypothesis that spelling

therapy gains will not only generalize to the spelling of untrained items but also to other language and cognitive functions that are subserved by the stimulated areas. In the same logic, we do not expect generalization to language and cognitive functions that have neural substrates different from the stimulated areas.

We further hypothesize that improvements related to tDCS or sham combined therapy may extend to increases in quality of life as measured by lifestyle activity. Research conducted by Dr. Carlson's lab (www.carlsonlab.org) using wearable accelerometers in community-dwelling older adults has demonstrated that low-intensity walking activity related to functional activities of daily living (shopping, vacuuming), were positively associated with several measures of health (self-report and performance-based measures of physical function, quality of life, depressive symptoms) independent of exercise activity (Varma et al., 2013). Low-intensity walking activity is associated with better health. Furthermore, greater daily walking activity was cross-sectionally associated with larger hippocampal volume, an important brain biomarker of memory and risk for dementia (Varma et al., 2015). We hypothesized that the language and other cognitive improvements related to intervention itself (either sham or tDCS) and especially language therapy may further correlate to increases in functional and social activities (e.g. walking to catch a bus, caretaking of grandchildren, and religious activities).

The imaging goal of this study is to develop molecular biomarkers for the effects of intervention using ^{1}H-MRS. Our aim is to investigate the molecular and cellular mechanisms of tDCS combined with spelling therapy in PPA. In a previous study using spectroscopy, individuals with PPA were found to have a specific neuropeptide signature different from other dementias and healthy controls (Catani et al., 2003), i.e. they had low levels of NAA. In the present study we intend to investigate the modulation of certain neuropeptides (NAA and GABA) from tDCS. Thus, application of tDCS is expected to increase the levels of NAA and NAA/Cre associated with better performance. Furthermore tDCS is expected to decrease the levels of GABA since anodal tDCS supposedly suppresses the inhibitory system suggesting a locally reduced activity of the GABA-ergic system (Stagg et al., 2011). In the present study we will investigate how tDCS combined with spelling interventions may change the NAA and GABA neurotransmitters' levels.

There is an increasing interest in evaluating the effects of deficits in synaptic transmission and in interventions targeting the molecular mechanisms of synaptic transmission. Recent aphasia studies have shown that the genetic information (specifically BDNF) may influence how tDCS modulates behavior (Fridriksson et al., 2018). This information is important because the BDNF gene may serve as a biomarker for those who have the potential to benefit from tDCS. Furthermore, there is evidence that tDCS modulates (increases) BDNF levels in blood plasma (Marangolo et al., 2014). If this is the case, then BDNF may be a molecular mechanism of tDCS. Given that there is a sex effect of BDNF levels (lower BDNF levels in women)(Chan & Ye, 2017; Dong et al., 2017), we seek to causally test the hypothesis that BDNF is the molecular mechanism of sex differences in frontotemporal dementia (FTD), specifically PPA, because it moderates and modulates tDCS effects. A better understanding of how BDNF moderates and modulates cognitive and language decline as well as tDCS effects in FTD will have a significant impact on the development of effective therapies. If BDNF is a possible endophenotype of cognitive decline in neurodegeneration, and its expression can be modulated by tDCS, this study will provide an exceptional molecular mechanistic target in the attempt to ameliorate cognition and delay the progression of FTD in the framework of personalized medicine. Results will serve as a foundation for multi-center clinical trials on BDNF as a mechanism for reversing neurodegeneration.

The PI and co-investigators have extensive research and clinical experience with all study tasks: behavioral language therapy (including spelling, naming, and repetition therapy; (Hillis, 1989, 1992, 1993) tDCS (e.g. (Yau et al., 2014)) cognitive evaluation of PPA (e.g. (Gorno-Tempini et al., 2011; Sepelyak et al., 2011) and spectroscopy (Gao et al., 2013; Rowland et al., 2012). We have recently completed a study on specifically applying behavioral therapy for the improvement of spelling abilities in both stroke and PPA

participants with encouraging preliminary results (Tsapkini & Hillis, 2013). We have documented the course and outcomes of grapheme-to-phoneme conversion treatment in two participants, one with stroke and another with PPA. We showed that the PPA patient could learn the phoneme-grapheme correspondences and showed a dramatic improvement in the phoneme-word associations as well. Other members of the study team have extensive experience with the use of tDCS (Dr John Desmond), spectroscopy (Dr Peter Barker) and genetic analyses (Dr. Avramopoulos) and will provide training to the PI and the other members who will be involved in the testing of participants.

3. Study Procedures

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

In summary, all participants will receive cognitive, speech, language, and detailed spelling evaluations as well as quality of life questionnaires. All participants will be chosen from Dr Hillis's database, one of the largest PPA databases in the country, and the ALS clinics and will be aware and have agreed to try to participate for the full length of the study, which may extend to three weeks for each experimental period. Then there will be a 2-week, 2-month and 6-month follow-up for individuals with PPA and 2-week and 2-month follow-ups for individuals with ALS. Each participant (except for those with ALS) will first be enrolled in the control condition for 12 weeks during which they will receive no intervention. They will receive language, cognitive and quality of life evaluations before and after this period. In this way they may serve as their own control and their own decline rate will be specified.

An additional group of 30 matched healthy controls will be recruited, mostly from the pool of spouses of participants in the tDCS study or matched controls from the Johns Hopkins community. They will be asked to 1) participate in behavioral evaluations of the same speech, language and cognitive assessments given to PPA,MCI, and ALS participants, 2) wear actigraphs to assess sleep, 3) have an MRI/MRS scan., and 4) participate in tDCS sessions combined with word learning training. Participation may involve multiple sessions and will be voluntary for any portion of the study.

Quality of Life questionnaires:
Participants will be administered standardized and non-standardized quality of life questionnaires before, after, and at follow-up intervals of each experimental period. The purpose of these questionnaires is to assess whether the proposed interventions have affected participants' well-being and the general quality of their life.

Language Tasks:
Patients will be administered baseline language and cognitive tasks, including 1 or more of the following, depending on their residual language and cognitive skills:
a) writing to dictation
b) oral spelling
c) oral and written naming of pictures
d) word-picture matching
f) written picture description
g) digit span
h) spatial span
i) verbal learning

Speech Tasks:
a) Speech/oral motor evaluation which is a routine part of a speech-language pathology evaluation that includes assessing range, strength, and speed or oral movements and speech intelligibility using the Frenchay Dysarthria Assessment (Enderby & Palmer, 2008) and the SIT

b) Acoustic measures of sustained phonation, fundamental frequency, jitter, shimmer, noise-to-harmonics ratio, pitch range/variation, loudness range/variation using PRAAT software
c) Speech articulation accuracy at the word, phrase, sentence, and paragraph level
Language Therapy tasks:

Spelling
Treatment of the PGC mechanism (PGC intervention)
For the PGC intervention, patients will receive language therapy of either phoneme-grapheme correspondence (PGC) or study of particular words (lexical therapy) or other similar type of therapy depending on the particular spelling deficit of each patient. Up to 30 English sounds will be selected representing most common word-initial English phonemes (speech sounds). Then a set of up to 30 English words starting with these sounds will be used as prompts to help the participants relate each sound to a grapheme (abstract letter identity or sequence of letter identities). In the case of spelling therapy with words, sets of up to 50 English words with matched psycholinguistic characteristics (frequency, length etc) will be chosen and divided in sets for either baseline testing, training, homework, or repetition. In the case of PGC therapy, the participant will be either asked to provide the letters that would correspond to each sound and if failed to do so will be provided with word prompts. In the case of lexical therapy, the participant will be asked to spell the chosen words and if failed to do so will be taught the spelling of each word in the training set or proceed to the rest of the set in other sets. Words or PGCs will be taught in blocks of 10; when the patient reaches criterion (80% correct) he or she will continue to the other blocks. Individuals who reach criterion quickly will move to a second stage, in which they will be asked to write words beginning with each target phoneme. They will be assisted in correcting the spelling of the words by "sounding out" the word. Baseline evaluation before each therapy session will be held before each therapy session and will either require that the participant would choose--from a series of possible initial letters or letter sequences of English written in front of him or her--the letter or letter sequence that corresponds to the phoneme the examiner provides each time.
Treatment of the lexical access mechanism (lexical access intervention).

For the lexical access treatment we will follow the methodology of the only other published spelling intervention in PPA (Rapp & Glucroft, 2009). Stimuli will consist of three word sets (n=10 for each set) that will be matched for lexical frequency, letter length, regularity, and concreteness. We will use 10 stimuli for each set to better match the PGC and lexical treatments. Set 1 will serve as trained items for the first condition (either sham or tDCS), and set 2 as untrained items and then set 2 will serve as trained items and set 3 as untrained. A spell-study-spell procedure (Beeson et al., 2013; Rapp & Glucroft, 2009) similar to that used in a number of other studies will be applied to the trained words, such that at every training session the patient will be asked: (1) to spell each word to dictation, (2) to study the word presented on a written note card and orally name each of its letters while the experimenter repeats the word, and (3) if the word has been spelled incorrectly to attempt to spell it again. This procedure will be repeated until the words of each set are correctly spelled for two consecutive sessions. If a word is spelled correctly on the first attempt, the word will still be presented for the participant to study and only then will the experimenter continue to the next word. Untrained words will be presented for spelling to dictation only at the time of the pre- and post-treatment evaluations and at two follow-ups to evaluate whether therapy gains generalize to the spelling of other words.

Naming
Individuals with word-retrieval deficits will have naming therapy, using either or both of the following therapies, depending on their severity of deficit and how fast they meet criterion for progression to the next level (100% accuracy on all trained stimulus sets).
Level 1: Naming actions, objects, or people from pictures using a cuing hierarchy (Hillis, 1989)

At each step, the participant attempts to retrieve the target word in response to a picture. If correct, the participant moves to the next picture after rehearsing the correct word multiple times. If incorrect, the participant is given the next cue.

1. Participant attempts to name target picture (for example, table).
2. Initial phoneme cue: “It starts with /t/.”
3. Rhyme cue: “It sounds like *fable.*”
4. Oral reading cue: Present word for oral reading.
5. Repetition cue: “Say table.”

Level 2:
Naming words in categories, given initial letters (after the game “Categories”). Participants will be given cards with category labels in rows, and initial letters as columns. The task will be to complete all cells as quickly as possible. The investigator/trainer will have “answer cards” and will be permitted to provide cues, allowing the participant half credit for each correct answer after cues. If the participant thinks of a word that is not on any of the answer cards he or she will get double “credit.” Cards are organized by level of difficulty, so that the participant progresses to more difficult categories and initial letters over time, trying to maintain both credit (accuracy without cues) and time. All categories on these cards are considered “trained” categories. Untrained categories will not be used in this training. We will evaluate word generation/fluency (naming words in a given semantic category, as quickly as possible in 1 minute), for both trained and untrained categories.

Working memory/repetition therapy
For individuals with working memory/repetition deficits we will follow a treatment that features a repetition intervention, as used previously in the literature (Marangolo et al., 2011; McNeil et al., 1995; Murray, 2012; Sung et al., 2009). Participants will be trained in a series of words or sentences of increasing complexity, i.e., words of increasing length and morphological structure (e.g., response- responsible- responsibility, or sentences of increasing length and structure ‘the girl hit the boy’- ‘the girl with the blue hat hit the boy’- ‘the girl with the blue hat hit the boy with the yellow sweater’). Ten triplets of words or sentences will be used as trained materials and another 10 triplets as untrained materials (evaluated at the beginning and end of treatment as well as at follow-up intervals). The treatment will involve the use of several steps which will progressively induce the patient to correctly reproduce the whole stimulus. In the beginning, the clinician speaks the whole stimulus and asks the patient to repeat it. If the patient correctly repeats the stimulus, the clinician will present another more complex stimulus, if he/she makes errors the clinician would move on the next step. In the next step, the clinician speaks the stimulus with a pause between each syllable—or word in the case of sentences—prolongs the vowel sound, exaggerates the articulatory gestures and asks the patient to do the same. The clinician repeats this step 3 times. If the participant succeeds, s/he is asked to repeat the stimulus 20 times without help. If the patient is not able to articulate the stimulus in the last step, the response is considered as an error. In this way we will be able to evaluate the performance and the progress of the participants for both the trained and untrained stimuli.

Computerized therapy
Participants undergoing computerized therapy will undergo initial assessments to establish their therapy objectives and subsequently determine the most appropriate application. Studies have indicated that the use of speech therapy apps can result in enhancements in language proficiency, confidence in communication, and overall quality of life among individuals with aphasia (Stark et al., 2015; Palmer et al., 2019). Furthermore, speech therapy apps and digital interventions have demonstrated potential in aiding individuals with dementia, particularly in enhancing language skills, mood regulation, and cognitive function (Lanza et al., 2021). These apps often incorporate features targeting diverse language domains, memory enhancement exercises, and functional activities. For individuals choosing to integrate cognitive behavioral therapy (CBT) into their speech or cognitive therapy regimen, we offer a structured framework focusing on cognitive restructuring, relaxation techniques, behavioral activation, problem-solving skills,

gratitude exercises, and more. These interventions are designed to facilitate their progress during the computerized therapy phase (Bilbrey et al. 2022).

Cognitive training exercises have been drawn from the computer aided cognitive training programs including BrainHQ (Posit Science, 2015), Tactus Therapy, and Constant Therapy. The efficacy of these tasks has been demonstrated for behavioral performance on a wide of variety cognitive tasks in clinical populations(Anderson et al., 2013), older adults ((Boggio et al., 2006, 2007; Fregni et al., 2006; Kang et al., 2009, Smith et al., 2009; Tennstedt & Unverzagt, 2013), and healthy individuals ((Roenker et al., 2003)). Improvements in behavioral performance have also been shown to be accompanied by changes in cortical, functional activity ((Berry et al., 2010; Rosen et al., 2011; Scalf et al., 2007). During each of the cognitive training sessions, patients will perform 4 tasks selected from the BrainHQ exercise series, designed to target processing speed and executive functions such as shifting, updating, monitoring, and manipulation. The combined tasks will take approximately 40 minutes to complete.

Novel Word-Learning
A "novel-word learning task" to be administered to healthy young and older adult participants is modelled after the task reported in Breining et al. (Breining et al., 2018). The task involves learning, over multiple sessions, the spoken names, written names and semantic features corresponding to a set of novel items, unfamiliar to the participants. Mirroring the protocols used with the PPA participants, healthy controls will receive tDCS or sham tCDS on different learning sessions in a double-blind, cross-over design and a similar statistical analysis approach will be used.

On each learning trial participants are presented with a picture of a novel (AI generated) item, its spoken name (e.g., "peejer"), its written name (e.g., PEAGER) and a short narrative in which various meaning features are presented (e.g., made of copper, used to harvest plants, etc.). Participants rehearse the information and are tested on recall and recognition at the beginning and end of each learning session.

Speech Therapy
The speech therapy protocol to address speech production includes over-articulation, drill/repetition at the single-word level, clinician modeling, cues for articulation placement, reading/formulating sentences with target words, and reading/formulating functional sentences. Consonant phonemes will be targeted in the initial, medial, and final positions of single words at the single word and sentence levels.

Assessment
Follow-up assessment will probe all sets of trained phoneme-grapheme correspondences, words, or other stimuli (e.g. sentences) to identify whether or not the patient has retained knowledge of the trained items. We will look at generalization effects (i.e. effects of training to untrained items). Differences in baseline measures in pre- and post-therapy accuracy for phoneme-grapheme correspondences for each patient will be evaluated using chi-square or Fisher's exact tests.
Participants will receive approximately 3-5 therapy sessions per week for 1-3 weeks for each stimulation site. There will be 1-6 stimulation sites depending on the characteristics of each individuals and their availability.

These measures will be performed at baseline and at follow-up to assess the effect of speech therapy with sham and real tDCS, and will include a speech/oral motor examination, the ALS-FRS-Revised (Cedarbaum et al., 1999), and the ASHA FACS, Communication Effectiveness Survey (Frattali et al., 1995).

tDCS methods:

Participants will take part in 5-15 consecutive training sessions (3-5 per week), each with a different tDCS condition/site of stimulation (see Table 1) separated by 2 months. Three pre-training sessions separated by 2 weeks, each with a different tDCS condition/site of stimulation (see Table 1), may be proposed to pre-test the tDCS montages. Anodal tDCS has typically been shown to up-regulate neuronal excitability and produce enhancement of behavioral performance. We hypothesize that anodal cerebral tDCS applied during behavioral therapy will enhance the therapeutic outcome relative to the sham tDCS condition as measured by the change from pre- to post-treatment accuracy in the trained task (e.g. number of correctly learned grapheme-phoneme correspondences, correctly named pictures, correctly named words in a given category) for trained and untrained stimuli. Previous tDCS protocols for acquisition of eyeblink conditioning using tDCS have received Johns Hopkins IRB approval. We will use either the same equipment as Dr John Desmond and his team have used (a Chattanooga Ionto Device) as well as the same application technique, recently acquired state-of-the-art device using special software for double-blinding (Soterix 1x1 CT: clinical trials), or a Neuroelectrics Starstim 8 device, which is a high-definition tDCS cap with higher precision. In order to administer intervention during the global pandemic and in a virtual manner, we will offer the option of remote stimulation (Soterix mini-CT device and MIND STIM+, YBrain). Attached please find letters from Clinical Engineering documenting that the tDCS devices have undergone clinical inspection as well as the manuals. When remote devices are implemented, participants and spouses will be trained prior to intervention and sessions will be conducted in real-time via video conference (e.g., Zoom). Stimulation will be delivered at an intensity of 1-2mA (estimated current density 0.04 mA/cm2; estimated total charge 0.048C/cm2) for a maximum of 20 minutes in the tDCS groups and for a maximum of 30 seconds in the Sham group. For both interventions (tDCS and Sham) the electrical current will be increased in a ramp-like fashion at the onset of the stimulation eliciting a transient tingling sensation on the scalp that usually disappears over seconds. Although the ramping process requires the researcher's input, it is now feasible to blind study staff who will be applying tDCS, as well as participants, as we now have a box that allows another member of the team to set the box to "tDCS" or "sham" without the knowledge of the researcher providing the therapy. In the Starstim 8 and remote devices, double-blinding is achieved through codes known only to the PI who is not administering any stimulation or evaluation, so both the technician or professional who administers the stimulation and evaluation are blind to the current condition being either actual tDCS or sham. After the ramping, in the sham condition, the intensity drops to 0 mA. These procedures have been shown to successfully blind participants as to whether they were members of experimental or control groups (Gandiga et al., 2006). The sites of tDCS application will be determined by the type of therapy used and the PPA variant group, MCI, or ALS and will be either the inferior frontal gyrus (IFG), the supramarginal gyrus (SMG), the middle temporal gyrus (MTG), the left precentral gyrus (PrCG) or a combination as shown in the literature. A recent meta-analysis of the functional neuroimaging literature on spelling has not yet identified clearly the neural substrates for PG conversion; the most plausible network includes the inferior parietal lobule including the supramarginal gyrus (Purcell et al., 2011).This area has also been identified as a critical area for spelling in the lesion literature as well. Another plausible area that shows activations during both PG conversion and lexical (word) spelling is the inferior frontal gyrus (IFG) (Purcell et al., 2011) and lesions in the IFG are associated with impaired PG conversion (Beeson et al., 2010). The stimulation site of IFG will be determined between F7 and F8 electrodes and that of SMG between TP3 and TP4 using the EEG 10-20 electrode position system (Homan, 1988). Additionally, studies have reported positive results of tDCS over the left dorsolateral prefrontal cortex (DLPFC) leading to improvement in attention deficits due to stroke, Parkinson's disease, and major depression (Boggio et al., 2006, 2007; Fregni et al., 2006; Kang et al., 2009). In addition to improving attention, anodal tDCS at the left DLPFC has been shown to improve working memory in TBI patients (Ulam et al., 2015). We hypothesize that anodal tDCS over the L DLPFC when administered in combination with cognitive training will improve language performance of PPA and MCI participants more than behavioral therapy alone, and that improvements may generalize to some other cognitive functions. The dependent variable will be the same baseline and post-therapy evaluation as described above that will take place before, after, 2 weeks and 2 months post-stimulation for each stimulation condition (see Table 1). These same areas, predominantly on the left, are activated during

naming (Jarso et al., 2013) and working memory (Philipose et al., 2007). In most cases of PPA and all cases of MCI, we will stimulate areas of the left hemisphere that are not atrophied. In the most advanced cases of PPA, with severe left hemisphere atrophy, we will stimulate the same sites in the right hemisphere in order to stimulate its compensatory mechanisms (see Hypothesis 1d). By this design we will be able to achieve a within-subject design for all conditions as well as to evaluate immediate, short- and long-term effects of each stimulation site without confounds and without any carry-over effects. We will also conduct a 6-month language evaluation to assess the overall therapy gains.

Spectroscopy methods:
MRSI will be performed using standard techniques on a 3T Achieva (Philips Healthcare Inc.) system equipped with a 32-channel head coil (InVivo). Metabolite concentrations will be measured from selected brain regions. The scanner will be operating within FDA allowed guidelines for RF power deposition, dB/dt, and acoustic noise at all times. The whole scanning session including acquisition of structural data as well as all spectroscopy sequences of interest will last about 1 hour. Scanning sessions will be performed at the beginning of enrollment, before and after each 5-day (or 15-day) tDCS treatment and at follow-up intervals for up to 8 sessions per participant over a period of 1.5 years. Spectroscopy data will be analyzed by members of the study-team from the Departments of Radiology and Biostatistics using standard procedures.

Plasma BDNF Methods:
Approximately ten ml of venous blood will be drawn into an EDTA tube and centrifuged to generate plasma. Pre-analytical factors for blood collection and storage for extracellular vesicles (EV) biomarkers analysis will be in accordance with published guidelines (see Witwer et al., 2013, 2017). Collection will take place in an outpatient lab at Johns Hopkins Bayview Medical Center by experienced staff.

Isolation and enrichment of plasma will follow the protocol published in Mustapic et al., 2017. Enzyme linked immunosorbent assays (ELISA) may be performed to quantify additional exploratory biomarkers. All analyses will be conducted by members in the Department of Genetic Medicine and Geriatric Medicine and Gerontology.

Saliva BDNF methods:
BDNF val66met rs6265 genotyping will be done by Taqman analysis of either the entire sample at the same time or at different timepoints. To genotype BDNF and APOE (genotype determined with 2 SNPs) by Taqman analysis we will purchase saliva tubes provided by DNA Genotek (oragen 500, DNA collection kits) and we will send them to participants homes with a paid return address at our lab. We will include those participants who had agreed to be contacted for future research.

Analyses
On careful consideration of the literature and consideration of the degenerative nature of the disease, its variability, and the poorly understood effects of tDCS we have selected a within-subject, cross-over design. This design is the one most commonly used in tDCS studies (below we discuss reasons for excluding a tDCS-only condition). Furthermore, in consultation with the 3 study team statisticians we evaluated whether this design would be appropriate given our preliminary data. As shown in preliminary study #1, the carry-over effect between the first period and the others is small and in this situation a cross-over design is recommended (Liang & Zeger, 1986). In the within-subject crossover protocol, each participant will be administered three experimental conditions: Control (natural progression), IFG tDCS+language (henceforth abbr. tDCS treatment) (word production) and sham tDCS+language (henceforth abbr. sham treatment). To achieve an accurate estimate of degeneration and rate of decline in each participant at their particular stage of the disease progression, each participant will first be enrolled in

the control condition (natural progression)**.** All analyses, behavioral and imaging, will be under the oversight of the study statisticians.

The genetic analysis will be done under the supervision of Dr. Avramopoulos and DNA samples will be provided by the Genetic Core facility at Johns Hopkins University. Based on previous research supporting that BDNF modulates tDCS outcome we will focus our analysis on the BDNF (/Val/Met polymorphism) and regulatory variants in closely functionally related genes. Final decisions will be made immediately before genotyping. To give an example, we may use the BDNF protein association network from the STRING functional protein association networks database (https://string-db.org/), a curated database providing valid expandable information on functional gene networks. Genetic variants that regulate these genes are then identified from public gene expression databases such as GTEx (https://gtexportal.org), which report variants whose genotype correlates strongly with gene expression across tissue types, i.e. they are expression quantitative trait loci – eQTLS).

Saliva samples will also be analyzed by the Genetic Core facility at Johns Hopkins University. DNA is setup in a format suitable for genotyping, called 'plating'. They will be genotyping all samples in one or more batches. Genotyping is completed using the most appropriate method for the polymorphism of interest. For the BDNF and APOE4 polymorphisms they will use Taqman analysis. Genotyping can be carried out in small batches or at the end of the study collection. At the end is most economical, small batches is costly). DNA is returned to the customer or can be stored long term in our biorepository for an annual fee.

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

Before any intervention participants receiving cognitive/language therapy will be enrolled in a control condition for 12 weeks during which no therapy will be provided to enable us to assess their personal decline rate. After this period they will be randomly assigned to either sham or tDCS experimental conditions. Participants receiving speech therapy will not complete the control condition because of potential decline in dysarthria in ALS, and will be randomized to either the sham or tDCS conditions upon enrollment. Three pre-training sessions may be proposed to test the tDCS experimental conditions before training. After 1-3 weeks of tDCS application (3-5 sessions in a week, 5-15 sessions per stimulation site) there will be an interval of approximately 2 months and then we will implement the other two tDCS conditions in a within-subject cross-over design, an example of which is shown in Tables1 and 2. We will follow-up the participants with PPA with 2-week, 2-month and a final 6-month follow-up sessions. For those with ALS, we will follow-up at 2-weeks and 2-months post treatment. For those participants who are long-distance, at the 2-week time point we may use a video conferencing tool such as GoToMeeting to administer the assessments. This is to mitigate the costs of travel for a short appointment. In these sessions we will administer the behavioral therapy assessment as described in the therapy section. We will test participants with both the practiced items and unpracticed items to look at generalization effects to untrained items. Given that we will test each participant in different conditions, an example of the sequence of conditions is shown in Tables 1 and 2.
After the final evaluation of interventions, we will offer an optional remote extension phase. This will consist of 18 additional months of intervention: 50 therapy sessions+tDCS (in 10 weeks) every 3 approximately months for a 18-month period, depending on availability, using different areas of stimulation (either the IFG, SMG, MTG, or DLPFC or Precuneus based on previous literature, see above in tDCS methods for details) for up to 18 months in total. We will complete another full evaluation of language and cognitive skills at the end of the stimulation phase. We will compare maintenance of therapy gains for individuals who participate in these remote sessions to those who do not, to answer the question whether tDCS effects may be extended beyond the initial 2-month period follow-up, up to 18 months and whether the rate of decline may change. This is very important because long periods of interventions and follow-up are needed in studying intervention outcomes in a neurodegenerative disorder.

Table 1: Timecourse of interventions (18 sessions) and evaluations for two groups of PPA participants in the crossover design (W: Week, IFG: inferior frontal gyrus, MTG: middle temporal gyrus, IPL: inferior parietal gyrus; eval (b+a): evaluation before and after or evaluation only; 18: number of sessions).

Time	W1-12	W14-20	W22-24	W27	W3-35	W38	W44	W61
Group 1: control then sham then tDCS	Control	1 sham 1 MTG 1 IPL 1 IFG	15 sham	2 week eval	15 IFG	2 week eval	2 month eval	6 m eval
Group 2: control then tDCS then sham	Control	1 sham 1 MTG 1 IPL 1 IFG	15 LIFG	2 week eval	15 sham	2 week eval	2 month eval	6 m eval
Both Groups	eval (b+a)	eval (b+a)	eval (b+a)	Eval	eval (b+a)	eval	Eval	Eval

Table 2: Timecourse of interventions (30 treatment sessions) and evaluations for two groups of participants (PPA and ALS) in the crossover design (W: Week, IFG: inferior frontal gyrus, LPRCG: left precentral gyrus)

Time	W1	W2-4	W7	W13	W14-16	W19	W25
Group 1: sham then tDCS	Baseline eval before phase 1	30 sham	2-week post phase 1 eval	2-month post phase 1 eval; baseline eval before phase 2 tx	15 IFG 15 PrGC	2-week post phase 2 eval	2-month eval post phase 2
Group 2: tDCS then sham	Baseline eval before phase 1	15 IFG 15 PrCG	2-week post phase 1 eval	2-month post phase 1 eval; baseline eval before phase 2 tx	30 sham	2-week post phase 2 eval	2-month eval post phase 2

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

Participants will be blinded to the application of anodal or sham tDCS. To achieve blinding, all participants will be fitted with the tDCS electrodes placed over the appropriate stimulation sites. As individuals typically experience a mild tingling sensation following the initiation of stimulation, both active and sham conditions will involve a ramping up of the current to appropriate intensity (1-2 mA) over 10-15 seconds to allow participants to habituate to the tingling sensation. At this point, the current will be ramped back down to 0 mA for individuals in the sham condition. Termination of the stimulation after the ramping up process is generally undetectable, and the brief duration of stimulation yields no functional effects. Staff who will be applying tDCS will also be blinded to the sham vs tDCS treatment condition.

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

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

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

All participants will be participants with PPA from Dr Hillis's database or participants with MCI from Dr. Hillis's clinic who will undergo active and sham conditions, thus serving as their own control.

f. Definition of treatment failure or participant removal criteria

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

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

When the study ends participants will continue to receive management with Dr Hillis and their neurologists in the Neuromuscular division as usual (follow-ups every 6 months with language and behavioral assessments). If a patient's participation in the study ends prematurely s/he will still receive care as before. In sum, termination of the study or termination of participation in it will not affect regular therapy he or she may be receiving.

4. Inclusion/Exclusion Criteria

Inclusion Criteria: Participants must be clinically diagnosed with svPPA, nfvPPA or lvPPA, unclassifiable PPA, MCI, or ALS. Diagnosis will be based on neuropsychological testing, language testing (most commonly the Western Aphasia Battery), MRI and clinical assessment. They must also be right-handed, speakers of English and have minimum a high-school education. For participants who are non-native speakers of English we may accept those who have less than a high-school education. Participants will be recruited from the Dr Hillis' PPA database, one of the largest in the country or from Dr. Hillis's clinic or may be referred by other clinicians with a confirmed diagnosis of PPA or MCI. ALS patients will be recruited from the ALS clinics. The age range of the participants will be 50-90 years old due to variability inherent in this neurodegenerative syndrome. Participants with ALS will have a diagnosis of definite, probable, or laboratory-supported probable ALS according to the EL Escorial revised criteria (Brooks et al., 2000). Participants with ALS will have scores as follows on the ALSFRS-R: 1-3 for "speech," 1-4 for "salivation," 0-4 for "swallowing," 2-4 for "dyspnea,", 2-4 for "orthopnea," 2-4 for "respiratory insufficiency". We will recruit individuals with ALS who are taking riluzole (or other ALS medications) or who have not started taking ALS medications, and we will use the medications as regressors.

Exclusion Criteria: Potential participants will be excluded if they have uncorrected visual or hearing impairment by self report or stroke/other premorbid neurological or psychiatric disorder affecting the brain, or any other language-based learning disorder other than PPA. Potential participants will also be excluded from the spelling treatment if they were not premorbidly proficient spellers. Furthermore, participants in advanced stages of the disease will be excluded since it has been shown that at these stages most language functions are very impaired (Sepelyak et al., 2011) and it will be difficult to see any results specific to the current therapeutic intervention. Furthermore, participants with pre-existing psychiatric disorders such as behavioral disturbances, severe depression, schizophrenia that do not allow them to comply or follow the study schedule and requirements such as repeated evaluation and therapy will be excluded. In addition, individuals with severe claustrophobia and cardiac pacemakers or ferromagnetic implants will be excluded from the MRI portion of the study since they may not tolerate the MRS sessions. Pregnant women will also be excluded. However, they could still participate in the treatment study without having the MRI scans.

Inclusion/Exclusion Criteria for Healthy Controls: For the behavioral assessment, actigraphy, and imaging (volumetric, connectivity and MRS analyses) portions of the study, we will need to compare our PPA patients to an age- and education-matched control group. Therefore, we will recruit a group of 75 participants, from the Johns Hopkins community. Healthy controls must be right-handed, 18-90 years old, speakers of English, and have at least high-school education and no neurological history outlined in the exclusion criteria above, including stroke, TIA, neurodegenerative disease, neurodevelopmental disorder, and TBI. For the MRI portion of the study, individuals with severe claustrophobia, cardiac pacemakers, or other magnetic implants may be excluded from the MRI portion of the study.

5. Drugs/ Substances/ Devices

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

tDCS has been established as a valid and reliable tool for at least temporarily affecting brain and behavior with minimal risks. Stimulation will be delivered by a battery-driven constant current stimulator (Chattanooga Ionto Device, Soterix 1x1 CT: clinical trials, Neuroelectrics Starstim 8 or Soterix mini-CT remote device or YBrain inc remote device). The stimulator is not connected to a mainline power source and cannot produce in excess of 4mA of current. In the case of remote stimulation, current is pre-determined and cannot be altered by participants (a distinct password is required). We will use non-metallic, conductive rubber electrodes covered by saline-soaked sponges to minimize the potential for chemical reactions at the interface of the scalp or skin and the electrodes.
We may also provide willing participants with accelerometers, i.e. small portable (at the wrist or ankle) devices that measure activity and sleep patterns or portable touch-screen devices. The accelerometers will be worn during the daily intervention periods, i.e., for 2-3 weeks in each period of every day visits for tDCS plus speech therapy or sham plus speech therapy. The portable touch-screens devices will be used for the participants who will opt for the booster training we are offering as an additional way to maximize their involvement and training.

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

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

6. Study Statistics

a. Primary outcome variable.

The primary outcome measures will be: a) change in performance from pre- to post-treatment levels on the trained items (e.g. change in % accuracy in phoneme-grapheme conversion of trained phonemes, % accuracy naming of trained pictures, average % correct names produced in trained categories in 1 minute), and, b) generalization to untrained items, measured by change in performance from pre- to post-treatment levels on the trained items (e.g. change in % accuracy in phoneme-grapheme conversion of untrained phonemes, % accuracy naming of untrained pictures, average % correct names produced in untrained categories in 1 minute). For those individuals with DLPFC stimulation for executive functions, we will use an additional automated score from BrainHQ program training (Smith et al., 2009). For individuals receiving home-based tDCS over the left perisylvian areas and their right hemisphere homologs, we will assess pre- to post- language scores. For individuals receiving speech therapy, we will assess pre- and post-speech measures listed above.

b. Secondary outcome variables.

Secondary outcome variables will be generalization of the improvement induced by the stimulation of IFG and SMG in other language and cognitive functions with the same neural substrates. Therefore, improvement may generalize to verbal working memory tasks such as sentence repetition and single digit

span backward and forward but will not generalize to functions that do not involve IFG, and SMG, such as picture association.

We are currently in the process of obtaining approval for a Data Use Agreement (DUA) through MYRAP, reference number MYRAP_00042373. We will be sharing: 1. multimodal MRI data: MPRAGE, resting-state fMRI, DTI of patients as well as healthy controls; 2. EEG data of the same participants; 3. demographic and behavioral data collected from the same participants. The data to be shared will adhere to all applicable privacy and confidentiality standards as outlined in the DUA. In specific, all direct identifiers (PHI) will be removed from the data set. A unique participant code will be used to link imaging and demographic data and the key to these codes will not be shared with the recipient. For the imaging data, the raw scans (.par/.rec) will be converted to .nii/.json files and dates will be removed for de-identification. Furthermore, volumetric MRI images will be defaced using specialized software tools from FreeSurfer. Freesurfer is pre-approved for defacing by the Johns Hopkins University Data Trust, ensuring it meets standards for safeguarding patient confidentiality. Defacing, in this context, involves detecting identifiable facial features (eyes, nose, ears, etc.) in the MRI scans, removing the facial features, and masking the regions where features are located. For other imaging scans the facemask can be removed by co-registering with the previously defaced volumetric MRI. This alignment allows for the transfer of defacing information from the functional MRI to other MRI images (i.e. resting-state).

Per the DUA the data will be shared with scientist Rajan Kashyap via OneDrive. The recipient will perform current flow simulations based on MRI, EEG, and behavioral data. The recipient will be sharing the simulation results and the outputs related to the project with the providing scientist. Data will be transferred electronically.

Additionally, we will be sharing data with Dr. Michael Petrides and his team at McGill University for the project titled, “Examination of diffusion MRI of patients and controls”. The data sharing will be captured by a Data Use Agreement with reference number MyRAP_00047387. The data to be shared will include: 1) Demographic and behavioral data for healthy controls and individuals with neurological impairment 2) MRI scans for T1, DTI, and rsfMRI. All data to be shared will be de-identified and adhere to all applicable privacy and confidentiality standards as outlined in the DUA. McGill will be preprocessing MRI data and will return JHU the data in ready or nearly ready status for statistical analysis. “Ready data” will be returned in excel format with measurements describing the brain structures of interest. “Nearly ready” data will be returned as preprocessed MRI data.

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

Design. This is a crossover trial, where each participant will be randomly assigned to receive either “IFG tDCS, then sham then SMG (in case a second stimulation site is implemented)” (group1) or “SMG then sham then IFG” or “sham then IFG then SMG”. In case a second stimulation site is not implemented participants will receive either sham and then tDCS (group 1) or tDCS and then sham (group 2). Based on previous studies regarding long-term effects of tDCS (see Fiori et al., 2011; Fridriksson et al., 2011; both looking at 3-weeks post-stimulation in participants with aphasia) and given the degenerative nature of PPA and ALS (and some cases of MCI), we assume that even though the effect of tDCS on the absolute level of the outcome may or may not persist at 2 weeks, the effect on the rate of decline persists no longer than 2 weeks. Analyses. The primary analyses will be a robust type of repeated measures Multivariate ANCOVA. Specifically, for each subject (i) and at follow-up times t=immediately after treatment, then 2 weeks and 2 months, we will consider the data $IFG_{t,i}$, $SMG_{t,i}$, $PrCG_{t,l,}$ and $S_{t,i}$; here, $IFG_{t,i}$ is the *change* of outcome from just before IFG tDCS treatment to time t after IFG tDCS treatment for subject i; and similarly for $SMG_{t,i}$, $PrCG_{t,i}$, and $S_{t,i}$ for tDCS and sham. For the behavioral methods, change of outcome is considered the difference (before and after therapy) of the independent measure of initial letter-sound associations learned and the change in SIT score. Then the research hypothesis that IFG (or SMG or

PrCG) treatment is superior to sham will be tested by testing the hypotheses that the distribution pr(R_{ti} - $S_{t,i}$) (or pr($L_{t,i}$ - $S_{t,i}$)) is not centered at zero. This will be done non-parametrically by obtaining the latter null distributions by the random permutation of the treatment labels (IFG, S, SMG, PrCG) of the data for each patient (Rosenbaum, 1988). The design effect, i.e., the ratio of sample sizes needed by an independence design vs. the crossover design to achieve a given power, depends on the correlations of outcomes across times and treatments. We have calculated that this crossover design with 30 participants and design effect of 1.5 has power 75% to detect an effect size of 0.8 between a tDCS site and sham treatment. In secondary analysis, we will use regression to examine if any effects of tDCS vary across participants with different characteristics such as age and atrophy volume. The present design allows us to evaluate the speech, language and neuromodulatory effects of both IFG,SMG, PrCG stimulation as well as speech or language therapy alone (in the condition of sham stimulation).

d. Early stopping rules. N/A

7. Risks

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

<u>tDCS</u>

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

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

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

<u>MR-spectroscopy</u>

The present study involves an optional portion in which a subset of participants undergo MRS scanning before and after each 1-3 weeks' tDCS therapy condition. This portion of the study will not be available to all participants (depending on funding for the MRI scans). The effects of undergoing MR scanning have been extensively studied and there are no risks associated with an MR or MRS exam. The patient may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. They will be asked to wear earplugs or earphones while in the magnet.

Other devices

Placing the accelerometers on the wrist or the ankle should have no potential risks as the elastic strap will be custom-fitted for each participant. Based on our administration of an accelerometer device from previous data collection, we have minimized these risks using a specially designed cloth pouch. It is possible that the presence of the accelerometer device around the wrist or ankle may be distracting. We have minimized this possibility through the use of custom pouches that have been worn around the ankle.

Biospecimen collection

Saliva

For saliva collection, we will purchase saliva tubes provided by DNA Genotek (oragen 500, DNA collection kits) and we will send them to participants homes with a paid return address at our lab. We will include those participants who had agreed to be contacted for future research. Genotyping will be carried out by the Johns Hopkins DNA Diagnostic Laboratory using standard methods including Taqman assays using an ABI7900HT apparatus.

Blood:

The present study involves an optional portion in which a subset of participants will have blood drawn for related research purposes before, after, and 6-months post therapy. Participants may feel some pain and discomfort at the needle entry site where blood is drawn, and there is a slight risk of bleeding or bruising around that site. There is also a remote risk of fainting after having blood drawn. To reduce the risk of injury because of a faint-related fall, participants will be closely monitored and asked about symptoms before they are allowed to stand up. Infection at the site of blood draw may occur.

Collection Protocol:

1. Source of blood: Median, cubital, basilic, or cephalic veins (never from a port or dorsum of hand). The maximum number of sticks (based on the participant's willingness) is 2 sticks each by 3 persons for a total of 6 sticks.
2. Tourniquet technique: Apply a tourniquet 2 inches above the antecubical fossa or above area to be drawn with enough pressure to provide adequate vein visibility. Have the patient form a fist. Select the site for venipuncture. Clean the forearm of the patient with antiseptic wipe in a circular motion beginning at the insertion site. Allow the antiseptic to dry. Anchor the vein by placing the thumb 2 inches below the site and pulling the skin taut to prevent the vein from moving. The holding finger is placed below the site, not above, to prevent accidentally sticking the finger with the needle. Using the dominant hand, insert either the vacutainer needle or the butterfly needle (if using vacutainer needle, attach hub first). Push the evacuated tube onto the vacutainer hub or the Luer adapter if using a butterfly. Release the tourniquet once blood flow is established. [The elapsed time for the tourniquet should be less than 1 minute. In the case that additional time is required, the tourniquet must be removed in a fashion that restores both the circulation and normal skin color.] Make sure that tube additives do not touch the stopper or the end of the needle during venipuncture.
3. Drawing blood into tubes: Pre-chill two 10 mL lavender-top K2 EDTA BD Vacutainer venous blood collection tubes (BD 366643, 10 mL plastic, whole blood EDTA tube with lavender top) on ice for at least 5 minutes. The redtop serum tubes stay at room temperature
4. Draw blood into redtop serum tube and store vertically at room temperature.
5. Completely fill two 10 ml EDTA lavender top tubes. Carefully remove the tubes when full without dislodging the needle.
6. Inversion of EDTA tubes: Immediately after allowing the lavender-top BD Vacutainer tube to completely fill, slowly and gently invert the tube 8-10 times. Immediately insert the tube into wet ice

7. Transport plasma EDTA lavender top tubes on ice and red top Serum tube at room temperature
8. Sample processing and freezing must be completed within 60 min of collection
*If blood draw is not successful, reason should be noted on the blood sample form
*Participant will be given a snack of juice and crackers or a granola bar after the blood draw procedure
Blood Sample Processing
1. Take lavender top tubes out of the ice box (See Figure 1 for appearance of tube at this step).
2. Centrifugation 1: (i) Within 30 minutes of collection, centrifuge at 2000 g for 10 min in a centrifuge. (ii) Collection of supernatant I - Transfer plasma (using Fisherbrand transfer 5.8 ml pipettes) to prechilled centrifugation tubes (BD 352196, 15 mL polypropylene Falcon tube), taking care to not disturb the buffy coat.
3. Centrifugation 2: (i) The secondary tubes are then centrifuged at 2000 g at 4C for 10 minutes to remove all potentially remaining cells (ii) While waiting for the centrifugation prepare labels and cryovials and pre-chill labeled cryovials in -80C freezer.
4. Collection of supernatant II
5. After second centrifugation, transfer the top approximately 4 ml of the
supernatant from each tube leaving behind about 500 ul (0.5ml) in the tube. Pipette the samples immediately after spinning. If there is not time immediately after spinning the sample, carefully place the tube in the refrigerator and process it no more than 2 hours after blood draw.
6. Place plasma labels on all microtubes and place plasma-labeled microtubes in a rack.
7. Using the 1 mL pipette, FROM THE TOP OF THE PLASMA FLUID, pipette 0.25 mL of the plasma into a 0.5 mL cryovials. The cryovials need to be prechilled in -80C freezer after labeling. Repeat until all serum is pipetted into microtubes. Leave the last 250 ul in the tube.
8. Put lids on all microtubes and place all aliquots in the -80freezer. Throw the rest of the blood sample and the tube into the biohazard container.
Buffy Coat:
· The plasma is removed, and the white cell layer is transferred with a clean plastic transfer pipette. It is acceptable to include some red blood cells in the sample; efforts to avoid red cells can lead to considerable loss of white cells and diminished DNA yield
· If the glycerol freezing solution is used the white cell layer should be added to an aliquot of the solution. Mix the cells and the solution gently by rocking the tube back and forth. Combining the buffy coat with an equal volume of the glycerol freezing solution is optimal (e.g., 1.0 ml of glycerol freezing solution to 1.0 ml of buffy coat from 20 ml of whole blood).

b. Steps taken to minimize the risks.

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

c. Plan for reporting unanticipated problems or study deviations.

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

Plan for dealing with incidental findings: All MRI scans will be read by a board-certified radiologist, Andreia Faria, MD (co-investigator). If unexpected abnormalities - incidental findings - are seen (which is unlikely, as every patient will have had a clinical MRI as part of their evaluation for PPA) the patient will be asked permission to contact the primary care physician about the abnormality, and will be offered a timely appointment with a neurologist (Argye Hillis, MD, co-investigator) if appropriate.

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

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

e. Financial risks to the participants.

No financial risk is involved. Only participants who are interested in trying language therapy with tDCS and can be in Baltimore—by themselves if they are capable of or with a family member if they are not capable of coming or staying by themselves in Baltimore—for the weekdays of therapy as well as the follow-up sessions will participate in the study.

8. Benefits

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

We cannot ensure that this research will provide any direct, sustainable benefit to the participants. It is possible that most participants will benefit from the present therapeutic intervention. Participants may or may not improve from the language therapy and this improvement may or may not generalize to other items or functions.

Completion of this project will result in better understanding whether and how tDCS coupled with behavioral therapy may help individuals with PPA or MCI with their language deficits. This project may provide a way to treat individuals with PPA or MCI, given that there is no proven treatment available to date.

9. Payment and Remuneration

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

Participants will not be paid to participate in the study. There is no penalty for not completing a tDCS or MRS session. Given available funding, participants may be reimbursed for parking, gas, meals and hotel expenses that may have occurred during the study for up to $2,700. Healthy controls will be compensated or at a rate of $20 per session for their participation.

10. Costs

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

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

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