Rehabilitating and Decelerating Language Loss in Primary Progressive Aphasia with tDCS Plus Language Therapy

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1. Abstract

Primary Progressive Aphasia (PPA) is a debilitating neurodegenerative disorder that causes a gradual worsening of language abilities. While there is a significant amount of research investigating multiple treatment approaches for individuals with aphasia resulting from stroke, individuals with PPA have far fewer treatment options to choose from. Due to the progressive nature of PPA, the main goal of PPA treatment is to decelerate the progression of decline in language function. PPA can be divided into three main variants that are defined based on their pattern of language impairment and patterns of atrophy: semantic PPA (svPPA), nonfluent/agrammatic PPA (nfvPPA), and logopenic PPA (lvPPA). While they each present with a specific pattern of language deficits, naming difficulties are present in all subtypes. Verb retrieval deficits are particularly prominent in nfvPPA while noun retrieval deficits are more common in svPPA (Hillis et al., 2006; Hillis, Oh, & Ken, 2004), individuals with lvPPA do not show differential noun/verb retrieval impairments (Thompson, Lukic, King, Mesulam, & Weintraub, 2012). The relatively few studies investigating treatments for naming in PPA have found positive treatment effects across all three variants where participants have been able to relearn words that were lost at baseline (Jokel, Rochon, & Anderson, 2010), maintain words they were able to name at baseline (Meyer, Getz, Brennan, Hu, & Friedman, 2016), and in some cases maintain these treatment effects for several weeks post-treatment (Jokel et al., 2010). While slowing the progression of language deterioration and maintaining language functioning is essential in PPA, treatment that generalizes to untreated items would provide the most benefit to patients. A handful of studies investigating the benefit of pairing language therapy with neurostimulation via tDCS of left IFG or transcranial magnetic stimulation (TMS) of dorsolateral prefrontal cortex (DLPFC) have found that generalization can occur and that the effects can last beyond therapy conclusion in PPA patients (Cotelli et al., 2014; Tsapkini et al., 2015; Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014). Studies in post-stroke aphasia have shown that applying anodal tDCS (A-tDCS), which excites neuronal activity (Nitsche et al., 2008) during naming therapy significantly improves word-retrieval compared to naming therapy alone (Baker, Rorden, & Fridriksson, 2010; Fridriksson, Richardson, Baker, & Rorden, 2011).

However, the tDCS studies in both post-stroke aphasia and PPA have focused on training items at the word-level, even though many studies of traditional language therapy in stroke-based aphasia have found that training complex items can generalize to simpler items (Kiran & Thompson, 2003; Mack & Thompson, 2017). According to the complexity account of treatment efficacy (CATE) training complex elements of language will lead to improvement in both complex as well as simpler elements of language (Thompson, Shapiro, Kiran, & Sobecks, 2003). Verb Network Strengthening (VNeST) treatment takes advantage of complexity theory by focusing on improving word retrieval deficits by having participants build sentences when targeting verbs and their related thematic roles (the nouns that serve as the doer of the action, the agent, and the receiver of the action, the theme). This treatment has been found to improve

sentence production, retrieval of trained verbs, and promote generalization to untrained verbs and nouns in post-stroke aphasia (Edmonds, 2016). VNeST has proven to be an effective treatment across all subtypes of post-stroke aphasia, including those with Broca's aphasia, which is associated with more difficulty with verb than noun production (Kim & Thompson, 2000). The added benefit of training more complex language elements, like sentences, to improve word-level deficits has not been sufficiently investigated in PPA. One case study investigating a discourse-level treatment in a man with PPA found that treating more complex language elements, such as discourse, can improve word-level deficits in PPA (Rogalski & Edmonds, 2008). Thus, it is likely that a treatment like VNeST, that focuses on generating sentences to improve word retrieval, would benefit individuals with PPA. We hypothesize that tDCS plus language therapy will be more beneficial for the improvement of word retrieval than sham plus language therapy.

2. Objectives (include all primary and secondary objectives)

Primary Objective: The primary objective of this study is to determine whether anodal (A-tDCS) applied to L IFG along with verb therapy can improve naming outcome in individuals with PPA. A randomized, double-blind, sham controlled, within-subject crossover design will be used because this allows each participant to serve as their own control. Participants will be randomly assigned to receive either a tDCS intervention period followed by a sham intervention period, or sham followed by tDCS. Participants will receive 15 training sessions within the tDCS intervention period and 15 sessions within the sham intervention period. Each participant will receive 3-5 sessions per week depending on their preference and availability. The tDCS and sham intervention periods will be separated by an 8 week "wash out period". Language will be evaluated before therapy, one week after therapy, and 8 weeks after therapy for each intervention period.

Aim 1: To evaluate the effects of A-tDCS applied to left IFG during VNeST therapy on word retrieval of trained verbs, and generalization to untrained verbs and nouns in a randomized double-blind, sham controlled, within-subject crossover trial design. The Object Action Naming Battery (OANB) (Druks, 2000) will be used to evaluate verb and noun retrieval by testing participants at baseline and at 1 and 8 weeks post-treatment. The OANB tests confrontational naming of 162 objects and 100 actions. The verbs on the OANB will be separated into trained (OANBtrained) and untrained (OANBuntrained) verbs, which will be personalized for each participant, in order to evaluate generalization. The primary outcome variable will be change in naming accuracy of OANBtrained verbs. Secondary outcome variables will be change in naming accuracy of OANBuntrained verbs and untrained nouns (OANBnouns), as well as

Hypothesis 1A. Anodal tDCS (A-tDCS) plus VNeST therapy (A-tDCS+therapy) will significantly improve word retrieval of trained transitive verbs (from baseline to 1 week and 8 weeks post treatment).
Hypothesis 1B. A-tDCS+therapy will generalize to other untreated verbs and nouns from baseline to 1 week and 8 weeks post treatment.
Hypothesis 1C. Combined A-tDCS+therapy will result in greater improvement in functional communication skills compared to sham+therapy.

Secondary Objective: The secondary objective of this study is to examine which patterns of atrophy predict the best response to treatment. This will help improve the selection of specific treatments for individual patients in the future.

Aim 2: To investigate which patterns of atrophy are associated with greatest response to treatment (improvement in naming verbs) in individuals with PPA following A-tDCS+therapy vs. sham+therapy.

Hypothesis: People with more IFG damage tend to have more trouble with verbs, so we predict they are likely to show the most change in verb naming following A-tDCS+therapy. It is possible that this hypothesis is incorrect, and they will show the least benefit from A-tDCS due to atrophy in IFG. It may be that people with more atrophy in other areas are going to benefit the most from this intervention.

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

PPA is a neurological syndrome characterized by the progressive impairment of language functioning caused by neurodegenerative diseases including frontotemporal lobar degeneration and Alzheimer's disease (Gorno-Tempini et al., 2011). In the early stages of PPA cognitive skills, like episodic memory, are typically preserved. There are three subtypes of PPA, which each have a different pattern of atrophy and distinct profile of language deficits. The semantic variant (svPPA) is defined by impaired naming and difficulty understanding single words, with preserved speech articulation, and is associated with bilateral atrophy in ventrolateral anterior temporal lobes that is typically greater in the left hemisphere. The non-fluent/agrammatic variant (nfvPPA) is characterized by agrammatic language production or apraxia of speech with atrophy in left posterior frontal and insular regions. Word comprehension is generally spared in the early stages of nfvPPA and lvPPA. Individuals with the logopenic variant (lvPPA) experience both word retrieval and sentence repetition deficits along with atrophy in left temporoparietal areas. Word retrieval deficits are present in the early stages of all PPA subtypes, although verbs tend to be more impacted in nfvPPA, and nouns in svPPA, with no distinction between nouns and verbs in lvPPA (Hillis et al., 2006, 2004; Thompson et al., 2012). This pattern is likely because verb retrieval is reliant on left frontal regions (den Ouden, Fix, Parrish, & Thompson, 2009). These debilitating language deficits interfere with daily life and therefore have many negative consequences for quality of life in PPA patients (Kortte & Rogalski, 2013). Yet, there are very few studies that have investigated language therapy to improve, or at the very least maintain word retrieval abilities, and ideally slow the progression of language loss. Although most of these studies have been single and dual case studies they do show that naming therapy can be used successfully in PPA and therefore more research is needed to determine which specific types of treatment will be most beneficial for individuals with different types of PPA. Thus far, approaches such as the picture naming repetition (Graham, Patterson, Pratt, & Hodges, 1999), reading and writing labels associated with pictures (Meyer et al., 2016), and generative naming where participants name members of a category (Beeson et al., 2011), have been found to be effective at maintaining language functions for a few months. Because PPA is a neurodegenerative disorder, and thus their language skills are expected to decline, reducing the rate of decline is an important goal.

The ultimate goal of most language interventions is for treatment effects to generalize to untrained items. Studies investigating complexity theory in post-stroke aphasia demonstrate that training more complex items in language therapy can generalize to simpler items. For example, several studies have found that training non-canonical sentences with complex syntax will generalize to untreated simpler syntactic structures (Mack & Thompson, 2017; Thompson et al., 2003) and training atypical exemplars during naming therapy will generalize to typical items but not vice versa (Kiran & Thompson, 2003). Evidence shows that VNeST therapy for word retrieval generalizes to untrained verbs and nouns, and improves sentence production as well (Edmonds, 2016). Participants are given transitive verbs, which require two arguments, that are used to build sentences by adding appropriate noun arguments that fulfill the thematic roles of the agent (the doer of the action) and the theme (the receiver of the action) (Edmonds et al., 2014). This type of therapy, which uses the building of sentences to treat word-level deficits, has not been investigated in PPA. Given the treatment success seen in individuals with post-stroke aphasia in terms of

generalization (Edmonds, 2016), it is important to investigate whether individuals with PPA could also benefit from this complexity strategy.

A growing number of studies investigating neurostimulation via tDCS have shown very promising results in post-stroke aphasia (Baker et al., 2010; Fridriksson et al., 2011). Similarly, the few studies investigating tDCS in PPA have also suggested it can augment the benefits of language therapy alone. For example, Tsapkini and colleagues (Tsapkini et al., 2015, 2014) have found that A-tDCS applied to left IFG paired with word-level spelling therapy improved written word production, and critically these effects generalized to untrained items and were sustained over the course of two months post-treatment conclusion.

In terms of examining the specific atrophy patterns that predict best response to language therapy in PPA, only two studies that we are aware of have examined this relationship (Cotelli et al., 2016; Meyer, Faria, Tippett, Hillis, & Friedman, 2017). In a study including all three PPA variants, Meyer and colleagues (2017) (Meyer et al., 2017) found that greater left temporal pole volume was associated with improved naming of untrained nouns, while greater left inferior temporal gyrus (ITG) volume was associated with more improvement in untrained nouns that were named incorrectly at baseline, but they did not examine effects of tDCS. Cotelli and colleagues (2017) (Cotelli et al., 2016) examined baseline gray matter volume in a group of individuals with nfvPPA who underwent treatment with tDCS + language therapy. Their results indicated that greater GM volume in left fusiform, left middle temporal, and right ITG was associated with improved object naming for trained items, while greater gray matter volume in left middle temporal gyrus was associated with improved action naming. Both of these studies investigated baseline atrophy patterns and their relation to treatment response utilizing word-level treatment paradigms focusing on nouns. Therefore, no studies of which we are aware have examined atrophy patterns and the prediction of treatment response for tDCS + language therapy for treatment focusing on verbs and sentences in PPA.

tDCS is a safe, non-invasive, and painless form of neurostimulation that involves applying a weak electrical current to the brain via two electrodes (the anode and the cathode) placed on the scalp. A low-intensity current is passed through these two electrodes to target specific areas of the brain. The anode enhances the likelihood of neuronal firing, likely due to depolarization of cortical neurons, whereas the cathode decreases the likelihood, likely due to hyperpolarization of cortical neurons (Nitsche et al., 2008). The cerebral excitability induced by tDCS can be long-lasting and last for up to several hours after tDCS administration (Nitsche et al., 2008). Research suggests the after effects of tDCS are induced through the modulation of sodium- and calcium-dependent channels and N-methyl-D-aspartate (NMDA)-receptor activity (Liebetanz & Liebetanz, 2002). Enhancing the neuronal firing rate via A-tDCS promotes mechanisms that underlie long-term potentiation (a persistent strengthening of synapses following stimulation of synaptic activity) and long-term depression (a reduction of synaptic activity). Both long-term potentiation and depression are critical for learning and memory. Moreover, research in healthy participants has shown one tDCS session modulates large-scale patterns of resting-state connectivity in brain regions close to the stimulation sites and in brain regions far from the stimulation sites (Keeser et al., 2011). In addition to the evidence demonstrating tDCS can reliably improve language outcomes in individuals with post-stroke aphasia, this technology allows a realistic sham stimulation, making it possible to carry out double blind clinical trials. In the sham condition, stimulation is applied for 30 seconds, and then rapidly ramped down. The participant generally only feels the first 30 seconds of real or sham stimulation, and so cannot distinguish the two conditions. The distinct timing of stimulation for sham versus real (20 minute) stimulation can be applied via the Soterix tDCS device, so that the experimenter also is blinded to the condition.

The aim of this proposed study is to study whether the combined benefits of training complex items (building sentences by training verbs and their thematic roles) and applying A-tDCS to left IFG to improve naming will result in significantly greater maintenance and generalization to untreated items and structures, compared to the same training with sham stimulation, in participants with PPA. This study also aims to investigate which patterns of atrophy in PPA are predictive of the best therapy outcomes, which will serve to improve the selection of specific treatments for individual patients in the future. Changes to functional communication skills will also be investigated.

4. Study Procedures

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

Study Procedures Overview

Study design overview: Participants will take part in 2 intervention periods of 15 training sessions (3-5 per week), with either tDCS + language therapy or sham+ language therapy, separated by 2 months. A computer-delivered naming treatment will be coupled with the stimulation. The computer-delivered treatment task will be 45-minutes in total length, so that it will commence at the same time as the tDCS administration and continue for another 25-minutes after the tDCS has ceased. All sessions, with the exception of the optional MRI, may take place at the participant's home or at a Hopkins site. When assessments and intervention are administered at the participant's home a study team member will perform the study procedure at home.

Visit 1: During the first visit, participants will undergo screening assessments. This will include tDCS and MRI safety screening. If the participant passes the initial screening portion, informed consent will be obtained. Neurological examination will also be performed (see below).

Visit 2: Participants may be asked to get MRI scanning, pending funding. Until funding is obtained, we will use MRI scans obtained for clinical purposes within 3 months of enrollment.

Visit 3-4: These sessions involve detailed language testing (see below) including computerized naming assessments. This battery will be the baseline language testing. A screening task will be administered prior to the baseline language testing. Participants must achieve at least 65% accuracy on screening task (comparable to treatment task) on 1 of 3 attempts. The screening test is administered to ensure that the participant understands the treatment task requirement. The probability that a patient will achieve >65% accuracy by chance on each of the three tries is low: $p<0.05$. If a participant is unable to reach this level of accuracy, study enrollment will be discontinued. A naming test will also be administered as part of baseline testing examining the ability to name nouns and verbs from pictures. Participants who's correct naming score exceeds an average of 80% accuracy will be excluded to leave at least a 20% improvement margin. That is, participants who already score close to ceiling may have limited room for naming improvement.

Visit 5-19: These sessions will involve the treatment sessions for the first intervention period. Prior to the start of treatment, participants will be randomly assigned to receive either " tDCS then sham" or "sham then tDCS". For example, if a participant is randomly assigned to received "tDCS then sham", the first intervention period of 15 sessions will be tDCS+ language treatment and the second intervention period will be 15 sessions of sham + language treatment.

Visit 20: This visit will involve 1 week post treatment language testing. This visit will be similar to Visits 3-4.
Visit 21: 8-week follow up visit. Testing during this session will be considered as baseline testing for phase 2 intervention.
Visit 22-36: These sessions will involve the treatment sessions for the second intervention period. The opposite tDCS condition will be implemented here. For example, if a participant is randomly assigned to received "tDCS then sham", the second intervention period will be 15 sessions of sham + language treatment.
Visit 37: 1-week follow up language testing after second intervention period.
Visit 38: 8-week follow up language testing after second intervention period.

Procedures for Screening (Visit 1)

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

Procedure for MRI Scanning (Visit 2)
Participants may receive MRI scanning to determine site of lesion. MRI will be performed pending funding. We will use clinical MRI (if available within 3 months of enrollment) until funding is obtained.

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

Language and cognitive tests will be administered to participants who pass the screening task. These tests will include:

1. Administer the Western Aphasia Battery-Revised (WAB-R): The WAB-R will characterize the participants' overall language impairment through the evaluation of the main clinical aspects of language functioning, including speech content, speech fluency, auditory comprehension, repetition, and naming. The WAB-R allows for the differentiation of these specific language abilities, as well as the classification of aphasia type. The WAB-R also yields a composite score, the Aphasia Quotient, which provides an overall measure of severity, in which lower scores denote more severe aphasia (Kertesz, 2007). Experimenters will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 30-45 minutes.

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

4. Administer the Northwestern Assessment of Verbs and Sentences (NAVS): The NAVS consists of five subtests: the Verb Naming Test (VNT), the Verb Comprehension Test (VCT), the Argument Structure Production Test (ASPT), the Sentence Production Priming Test (SPPT), and the Sentence Comprehension Test (SCT) (Thompson, 2012). The VNT and VCT examine production and comprehension of isolated verbs that differ with respect to their argument structure. The ASPT evaluates production of these verbs together with their arguments in a sentence production task. Verb argument structure and optionality effects are examined using verb types (i.e., one-, two-, and three-argument verbs) as singletons (i.e., in the VNT and VCT) and in a sentence context (i.e., in the ASPT). Production and comprehension of sentences by canonicity and sentence type are examined in the SPPT and the SCT, respectively, using six sentence types (i.e., three canonical forms: active, subject extracted wh-question (SWQ), and subject relative clause (SR); three noncanonical forms: passive, object extracted wh-question (OWQ), and object relative clause (OR)). Experimenters will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 30-60 minutes.

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

6. Administer the Pyramids and Palm Trees Test (PPTT) (Short form): The PPTT is a test of semantic processing. This test assesses the degree to which a participant can access meaning from pictures. Information from the test will help determine whether a participant's difficulty in naming or pointing to a named picture is due to a difficulty in retrieving semantic information from pictures (Breining et al., 2015; Howard & Patterson, 1992). Experimenters will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-20 minutes.

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

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

9. Administer the Object & Action Naming Battery (OANB) (see section below on Naming Assessments): The OANB consists of line drawings of 162 objects and 100 actions together with ratings for age-of-acquisition, familiarity and imageability of the verbal labels of the pictures (Druks, 2000). Experimenters will refer to the manual for explicit instructions regarding administration and scoring

procedures. Administration time will range between 30-60 minutes. Participants whose correct naming score exceeds an average of 80% on the OANB during baseline sessions will be excluded, in order to leave at least a 20% improvement margin. That is, patients who already score close to ceiling may have limited room for naming improvement as measured by the OANB.

Procedures for the Naming Assessments (Visits 1, 2 & all follow up evaluations)
The following procedures will be performed during Visits 1, 2, and each follow-up evaluation:
1. Turn on the laptop computer and position in front of the participant.
2. Set up and start internal web-camera for audio-visual recording, to allow inter-rater reliability assessment. Administer the OANB. Instruct the participant to overtly name each picture as soon as it is displayed. Trials will end following a response or after 10-seconds have elapsed, in which the administrator will say the correct picture name in order to discourage perseveration on subsequent trials.
3. Stop web-camera and save video file for later scoring of naming.

Procedures for the "Cookie Theft" Picture Discourse Analysis and Depression Scale (Visit 3, 20, 21, 37 and 38). The following procedures will be performed during Visits 3 (baseline), 20 (1-week after intervention period 1), 20 (8-week follow up/baseline testing for intervention period 2), 37 (1-week after intervention period 2), and 38 (8-weeks after intervention period 2).

1. The "Cookie Theft" is to be completed following the administration of the naming assessments, so the laptop computer and web-camera set-up will need to remain for this portion of the assessment.
2. Place the Cookie Theft picture in front of the participant.
3. Tell the participant, "Tell me everything you see going on in this picture. Whenever possible try to use full sentences.
4. Stop web-camera and save video file for later transcription.

Procedures for Treatment (Visit 5-19) for intervention period 1 and Visits 22-36 for intervention period 2

The following procedures will be performed:

1. Place a scalp cap, which contains scalp sites labeled according to the 10-20 system, on participant's head. Locate the "F5" label, which is the label corresponding to the left IFG.
2. Soak the 2 sponge electrodes in saline solution and place inside rubber electrode holders.
3. Place the anode electrode under the designated area ("F5") against the scalp, and reference electrode on the right deltoid muscle.
4. Connect the electrode cables to the Soterix tDCS device.
5. Start the tDCS device and enter the code. Soterix clinical trial tDCS device includes a software for true operator blinding where the PI can have preset codes for tDCS and sham trials including the dosage and the clinician will enter the codes and the device will present either tDCS or sham depending on the code that was assigned.
6. Set-up the computer-delivered language task: Turn on computer/ipad and position in front of participant. Plug in the red/green response buttons into the computer and position in front of participant. Locate the participant's designated treatment folder and open.
7. Instruct the participant how to perform the self-administered computer-delivered naming treatment, consisting of a picture/seen and heard spoken word verification task, which will be coupled with the stimulation. The computerized treatment task will be 45-minutes in total length, so that it will commence at the same time as the tDCS administration. A picture will be presented for 2 s on a laptop computer screen and will be immediately followed by an audio-visual display of a female speaker's mouth saying a

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

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

Participants will receive treatment for 3-5 weeks (3-5 sessions in a week: total 15 sessions) for each of the intervention period. There will be 1 tDCS treatment period and 1 sham treatment period for each participant. We will follow-up the participants with 1-week and 8-week follow-up sessions after each treatment period. Study duration will be approximately 6 months and the number of visits for each participant will be 38. See Figure 1:

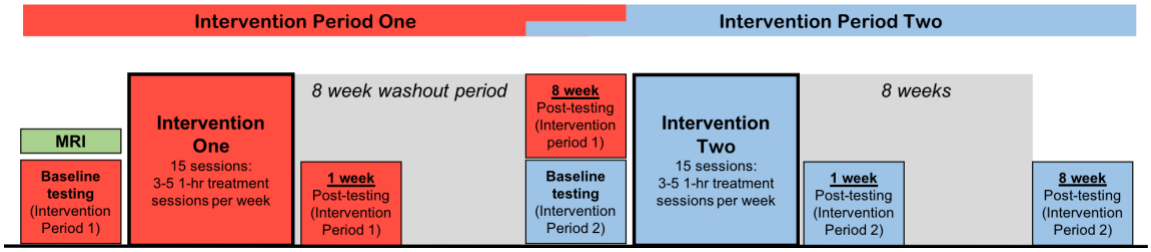

Figure 1. Study Design

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

Randomization and Blinding

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

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

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

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

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

f. Definition of treatment failure or participant removal criteria.

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

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

When the study ends participants will continue to receive management with Dr. Hillis or their own neurologist as usual (generally follow-up visits every about 6 months). 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.

5. Inclusion/Exclusion Criteria

Participants in this study will have Primary Progressive Aphasia. Diagnostic evaluations will be conducted during the participants' initial visit to confirm aphasia diagnosis.

Inclusion Criterion:
1) Diagnosis of PPA, based on the PPA criteria (Gorno-Tempini et al., 2011) and presence of naming deficits
2) Capable of giving informed consent or indicating another to provide informed consent
3) 18 years of age or older.
4) Able to participate in language therapy tasks

Exclusion Criterion:
1) Did not speak English before the age of five
2) Less than 10 years of education
3) Not medically stable
4) Picture naming ability below 10%
5) Picture naming ability above 85%
5) Significant history of drug or alcohol abuse or psychiatric or neurologic problems affecting the brain (other than PPA)
6) Non-MRI compatible pacemaker, implanted ferrous metal, claustrophobia, or other MRI contraindication
7) Seizures during the previous 12 months
8) Uncorrected visual loss or hearing loss by self-report
9) Use of medications that substantially lower the seizure threshold (e.g., methylphenidate) or use of NMDA antagonists (e.g., memantine)
10) History of brain surgery or any metal in the head
11) Scalp sensitivity (per participant report).

6. Drugs/ Substances/ Devices

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

tDCS has been established as a valid and reliable tool for at least temporarily affecting brain and behavior with minimal risks. Stimulation will be delivered by a battery-driven constant current stimulator (Soterix device, or a comparable model). The stimulator is not connected to a mainline power source and cannot produce in excess of 4mA of current. We will use non-metallic, conductive rubber electrodes covered by

saline-soaked sponges to minimize the potential for chemical reactions at the interface of the scalp or skin and the electrodes.

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

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

7. Study Statistics

a. Primary outcome variable

The primary outcome variable will be trained verbs on the OANB (OANBtrained) (pre-treatment and 1-week post-testing). To assess change in naming ability, the primary outcome in this study, the OANB) will be administered.

b. Secondary outcome variables

We will evaluate the effect of tDCS versus sham on change in naming of untrained verbs and nouns, and determine which pattern of atrophy is associated with the best treatment outcome.

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

Statistical Analyses

For Aim 1, Hypothesis 1a This hypothesis states that Anodal tDCS (A-tDCS) plus VNeST therapy (A-tDCS+therapy) will significantly improve word retrieval of trained transitive verbs (from baseline to 1 week and 8 weeks post treatment). In the proposed study each participant will either receive tDCS (T) in the first intervention period followed by sham (S) in the second period (order = TS), or they will receive sham in the first period followed by tDCS (order = ST). For each participant, i, we will measure the change in word retrieval on the OANBtrained due to real tDCS stimulation by subtracting word retrieval performance accuracy on the OANBtrained before tDCS stimulation from the testing period 1 week following tDCS stimulation (δYi,tDCS). The identical measure will be computed for sham stimulation (δYi,sham). The data will be analyzed (order$i$, δYi,tDCS, δYi,sham) for participants $i = 1,\ldots,n$. Three models will be evaluated: the model of tDCS vs. sham, the model that adds the period effect, and the model that adds the interaction (a carryover effect). The predictive accuracy of these 3 models will be compared using the leave-one-out cross-validation R^2. The model that best fits the data (the model with the highest R^2) will then be used to estimate the effect of tDCS relative to sham. This procedure will be repeated to determine changes from baseline to a period 8 weeks after treatment conclusion.

Sample Size Determination

We expect to enroll at least 50 participants with PPA over five years, and expect 45-50 will complete the study. This sample size is based on data collected from a separate study, IRB protocol number NA_00078932, PI Kyrana Tsapkini. T*he effect size for anodal tDCS stimulation was 0.6 for trained items and 1.5 for untrained items.* We determined the number of participants to study, in order for the analysis to have 80% power to detect an effect size as low as 0.6. Allowing for 10% attrition, a sample size of 50 was chosen.

Missing Data

We plan to minimize missing data by avoiding prolonged intervals between stimulations: 2 months may seem long with regard to the literature, but it is a reasonable length of time to be able to determine sustainability of any therapy. To minimize possible biases, analyses will be by intention to treat; any missing data will be addressed with the technique of multiple imputation (Rubin, 2004), generally recognized as best for handling missing data (Little et al., 2012).

Secondary Analyses

For Aim 1, Hypothesis 1b This hypothesis states that A-tDCS+therapy will generalize to other untreated verbs and nouns from baseline to 1 week and 8 weeks post treatment. The analyses will be identical to those described for Aim 1, Hypothesis 1a, except data from untreated verbs (OANBuntrained) and OANBnouns (untrained) will be used.

Aim 1, Hypothesis 1c Hypothesis 1c states that combined A-tDCS+therapy will result in greater improvement in functional communication skills compared to sham+therapy. Changes to functional communication skills resulting from A-tDCS+therapy vs. sham will be assessed using the ASHA FACS scale.

For Aim 2, Hypothesis 1: The proposed study aims to determine which patterns of baseline atrophy will predict the best response to A-tDCS plus a verb treatment using sentence building in individuals with PPA. People with more IFG damage tend to have more trouble with verbs, so we predict they are likely to show the most change in the primary outcome variable (OANBtrained verbs) with A-tDCS+therapy. It is possible that this hypothesis is incorrect, and they will show the least benefit from tDCS due to atrophy in IFG. It may be that people with more atrophy in other areas are going to benefit the most. Confirmation of either hypothesis will help select the best candidates for treatment. The area of peak atrophy (greatest difference between volume of each of the parcels on the JHU-MNI atlas in the participant compared to controls) will be identified for each participant. We will group participants by area of peak atrophy, and compare groups for each outcome variable, using Kruskal-Wallis one-way analysis of variance, for each outcome variable. As an exploratory analysis, we will also evaluate Spearman's correlations between the primary outcome variable and baseline volume in 5 regions of interest (areas affected in PPA: left IFG, left inferior temporal gyrus, left temporal pole, left superior temporal gyrus, and left supramarginal gyrus).

d. Early stopping rules. N/A

8. Risks

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

tDCS

The present study involves application of transcranial direct current stimulation. Weak direct currents can be applied non-invasively, transcranially and painlessly (Nitsche et al., 2003). This is a non-invasive and painless technique that leads to transient changes in cortical excitability that are fully reversible (Nitsche, Liebetanz, Tergau, & Paulus, 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 (Gandiga, Hummel, & Cohen, 2006; Nitsche et al., 2003, 2004)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 (Nitsche et al., 2004)
- No changes in diffusion weighted or contrast-enhanced MRI and in EEG after exposure to tDCS

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

MRI

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

b. Steps taken to minimize the risks.

Participants will be carefully screened over the phone prior to being scheduled, to assure that they meet study criteria. tDCS stimulation will be ramped up over the first 30 seconds of stimulation in order to eliminate the sensation of tingling that can occur under the electrodes during the initial moments of tDCS application. The participant may stop testing or the intervention any time. There will be emergency personnel and equipment on hand for the participants' 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 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: MRI scans will be read by a radiologist. If an incidental finding is discovered, the site PI (Dr. Hillis) will call the patient, and arrange to see the patient in clinic on a timely basis to discuss the finding and the plan for medical follow-up (if any). As Dr. Hillis is the neurologist of the PPA patients, she will provide care for most of the findings seen on brain MRI, but will refer the patient to neurosurgeons or other physicians as appropriate.

On any given session, if the patient experiences significant frustration, anxiety, or fatigue, that session may be terminated early.

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

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

9. Benefits

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

We cannot ensure that this research will provide any direct, sustainable benefit to the participants. It is possible that most participants will benefit from the present therapeutic intervention. Participants may or may not 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 language therapy may help individuals with PPA with their language deficits. This project may provide a way to treat individuals with PPA given that there is no proven treatment available to date.

10. Payment and Remuneration

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

Participants will not be paid to participate in the study. There is no penalty for not completing a tDCS or MRS session. Given available funding, participants may be reimbursed for parking, gas, meals and hotel expenses that may have occurred during the study

11. Costs

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

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

12. References

Baker, J. M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*, *41*(6), 1229–36. https://doi.org/10.1161/STROKEAHA.109.576785

Beeson, P. M., King, R. M., Bonakdarpour, B., Henry, M. L., Cho, H., & Rapcsak, S. Z. (2011). Positive Effects of Language Treatment for the Logopenic Variant of Primary Progressive Aphasia. *Journal of Molecular Neuroscience*, *45*(3), 724–736. https://doi.org/10.1007/s12031-011-9579-2

Breining, B. L., Lala, T., Cuitiño, M. M., Manes, F., Peristeri, E., Tsapkini, K., … Hillis, A. E. (2015). A brief assessment of object semantics in primary progressive aphasia. *Aphasiology*, *29*(4), 488–505. https://doi.org/10.1080/02687038.2014.973360

Cotelli, M., Manenti, R., Paternicò, D., Cosseddu, M., Brambilla, M., Petesi, M., … Borroni, B. (2016). Grey Matter Density Predicts the Improvement of Naming Abilities After tDCS Intervention in Agrammatic Variant of Primary Progressive Aphasia. *Brain Topography*, *29*(5), 738–751. https://doi.org/10.1007/s10548-016-0494-2

Cotelli, M., Manenti, R., Petesi, M., Brambilla, M., Cosseddu, M., Zanetti, O., … Borroni, B. (2014). Treatment of Primary Progressive Aphasias by Transcranial Direct Current Stimulation Combined with Language Training. *Journal of Alzheimer's Disease*, *39*(4), 799–808. https://doi.org/10.3233/JAD-131427

den Ouden, D.-B., Fix, S., Parrish, T. B., & Thompson, C. K. (2009). Argument structure effects in action verb naming in static and dynamic conditions. *Journal of Neurolinguistics*, *22*(2), 196–215. https://doi.org/10.1016/j.jneuroling.2008.10.004

Druks, J. (2000). *Object and action naming battery*. Hove: Psychology Press. Retrieved from http://discovery.ucl.ac.uk/87465/

Edmonds, L. A. (2016). A Review of Verb Network Strengthening Treatment: Theory, Methods, Results, and Clinical Implications. *Topics in Language Disorders*, *36*(2), 123. https://doi.org/10.1097/TLD.0000000000000088

Edmonds, L. A., Mammino, K., & Ojeda, J. (2014). Effect of Verb Network Strengthening Treatment (VNeST) in Persons With Aphasia: Extension and Replication of Previous Findings. *American Journal of Speech-Language Pathology*, *23*(2), S312–S329. https://doi.org/10.1044/2014_AJSLP-13-0098

Fridriksson, J., Richardson, J. D., Baker, J. M., & Rorden, C. (2011). Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. *Stroke*, *42*(3), 819–21. https://doi.org/10.1161/STROKEAHA.110.600288

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *117*(4), 845–50. https://doi.org/10.1016/j.clinph.2005.12.003

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., … Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006–14. https://doi.org/10.1212/WNL.0b013e31821103e6

Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. *Neuropsychology*, *13*(3), 359–380.

Hillis, A. E., Heidler-Gary, J., Newhart, M., Chang, S., Ken, L., & Bak, T. H. (2006). Naming and comprehension in primary progressive aphasia: The influence of grammatical word class. *Aphasiology*, *20*(2–4), 246–256. https://doi.org/10.1080/02687030500473262

Hillis, A. E., Oh, S., & Ken, L. (2004). Deterioration of naming nouns versus verbs in primary progressive aphasia. *Annals of Neurology*, *55*, 268–275.

Howard, D., & Patterson, K. E. (1992). *The Pyramids and Palm Trees Test: A test of semantic access from words and pictures*. Thames Valley Test Company.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. M. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology*, *64*(5), 872–5. https://doi.org/10.1212/01.WNL.0000152986.07469.E9

Jokel, R., Rochon, E., & Anderson, N. D. (2010). Errorless learning of computer-generated words in a patient with semantic dementia. *Neuropsychological Rehabilitation*, *20*(1), 16–41. https://doi.org/10.1080/09602010902879859

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston Naming Test*. Pro-ed.

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., … Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(43), 15284–93. https://doi.org/10.1523/JNEUROSCI.0542-11.2011

Kertesz, A. (2007). *Western Aphasia Battery - Revised*. San Antonio, TX: Harcourt Assessment, Inc.

Kim, M., & Thompson, C. K. (2000). Patterns of Comprehension and Production of Nouns and Verbs in Agrammatism: Implications for Lexical Organization. *Brain and Language*, *74*(1), 1–25. https://doi.org/10.1006/brln.2000.2315

Kiran, S., & Thompson, C. K. (2003). The Role of Semantic Complexity in Treatment of Naming Deficits: Training Semantic Categories in Fluent Aphasia by Controlling Exemplar Typicality. *Journal of Speech, Language, and Hearing Research*, *46*(4), 773–787. https://doi.org/10.1044/1092-4388(2003/061)

Kortte, K. B., & Rogalski, E. J. (2013). Behavioural interventions for enhancing life participation in behavioural variant frontotemporal dementia and primary progressive aphasia. *International Review of Psychiatry*, *25*(2), 237–245. https://doi.org/10.3109/09540261.2012.751017

Liebetanz, D., & Liebetanz, D. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*(10), 2238–2247. https://doi.org/10.1093/brain/awf238

Little, R. J., D'agostino, R., Cohen, M. L., Dickersin, K., Emerson, S. S., Farrar, J. T., … Murphy, S. A. (2012). The prevention and treatment of missing data in clinical trials. *New England Journal of Medicine*, *367*(14), 1355–1360.

Mack, J. E., & Thompson, C. K. (2017). Recovery of Online Sentence Processing in Aphasia: Eye Movement Changes Resulting From Treatment of Underlying Forms. *Journal of Speech, Language, and Hearing Research*, *60*(5), 1299–1315. https://doi.org/10.1044/2016_JSLHR-L-16-0108

Meyer, A. M., Faria, A. V., Tippett, D. C., Hillis, A. E., & Friedman, R. B. (2017). The relationship between baseline volume in temporal areas and post-treatment naming accuracy in primary progressive aphasia. *Aphasiology*, *31*(9), 1059–1077. https://doi.org/10.1080/02687038.2017.1296557

Meyer, A. M., Getz, H. R., Brennan, D. M., Hu, T. M., & Friedman, R. B. (2016). Telerehabilitation of anomia in primary progressive aphasia. *Aphasiology*, *30*(4), 483–507. https://doi.org/10.1080/02687038.2015.1081142

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., … Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/J.BRS.2008.06.004

Nitsche, M. A., Liebetanz, D., Tergau, F., & Paulus, W. (2002). Modulation of cortical excitability by transcranial direct current stimulation. *Der Nervenarzt*, *73*(4), 332–335.

Nitsche, M. A., Niehaus, L., Hoffmann, K. T., Hengst, S., Liebetanz, D., Paulus, W., & Meyer, B. U. (2004). MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. *Clinical Neurophysiology*, *115*(10), 2419–2423. https://doi.org/10.1016/j.clinph.2004.05.001

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of Implicit Motor Learning by Weak Transcranial Direct Current Stimulation of the Primary Motor Cortex in the Human. *Journal of Cognitive Neuroscience*, *15*(4), 619–626. https://doi.org/10.1162/089892903321662994

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*(4), 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004

Rogalski, Y., & Edmonds, L. A. (2008). Attentive Reading and Constrained Summarisation (ARCS) treatment in primary progressive aphasia: A case study. *Aphasiology*, *22*(7–8), 763–775. https://doi.org/10.1080/02687030701803796

Rubin, D. B. (2004). *Multiple imputation for nonresponse in surveys* (Vol. 81). John Wiley & Sons.

Thompson, C. K. (2012). *Northwestern Assessment of Verbs and Sentences (NAVS)*. Retrieved from https://www.scholars.northwestern.edu/en/publications/northwestern-assessment-of-verbs-and-sentences-navs

Thompson, C. K., Lukic, S., King, M. C., Mesulam, M. M., & Weintraub, S. (2012). Verb and noun deficits in stroke-induced and primary progressive aphasia: The Northwestern Naming Battery. *Aphasiology*, *26*(5), 632–655. https://doi.org/10.1080/02687038.2012.676852

Thompson, C. K., Shapiro, L. P., Kiran, S., & Sobecks, J. (2003). The Role of Syntactic Complexity in Treatment of Sentence Deficits in Agrammatic Aphasia: The Complexity Account of Treatment Efficacy (CATE). *Journal of Speech, Language, and Hearing Research*, *46*(3), 591–607. https://doi.org/10.1044/1092-4388(2003/047)

Tsapkini, K., Chakravarty, T., Webb Vargas, Y., Lindquist, M. A., Frangakis, C. E., & Hillis, A. E. (2015). Effects of different language and tDCS interventions in PPA and their neural correlates. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/conf.fpsyg.2015.65.00034

Tsapkini, K., Frangakis, C., Gomez, Y., Davis, C., & Hillis, A. E. (2014). Augmentation of spelling therapy with transcranial direct current stimulation in primary progressive aphasia: Preliminary results and challenges. *Aphasiology*, *28*(8–9), 1112–1130. https://doi.org/10.1080/02687038.2014.930410