ABSTRACT

Title of Thesis: THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON NARRATIVE ABILITIES IN PRIMARY PROGRESSIVE APHASIA

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Transcranial direct current stimulation (tDCS) is a neuromodulation technique that has recently been studied as an adjunct to speech-language therapy in persons with primary progressive aphasia (PPA). Preliminary studies have shown improved language abilities with tDCS-supplemented therapy, primarily in naming, as well as improved generalization and maintenance of skills. However, the effects of tDCS on narrative abilities have not yet been well studied in this population. The present study examined whether the addition of tDCS to anomia therapy improved narrative language measures in 16 participants with PPA versus sham stimulation plus therapy. Results demonstrated that tDCS did not significantly improve narrative language measures in participants with PPA.

THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON NARRATIVE ABILITIES IN PRIMARY PROGRESSIVE APHASIA

by

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Introduction

Primary progressive aphasia (PPA) is a disorder in which language abilities progressively decline due to neurodegenerative disease (Gorno-Tempini et al., 2011; Mesulam, 2001, 2007). Persons with PPA initially show only language deficits, with other cognitive functions left relatively intact at onset. PPA often arises from frontotemporal lobar degeneration (FTLD), a disease process involving progressive damage to the frontal and temporal lobes of the brain (Grossman, 2010). Neuroimaging studies have shown asymmetrical perisylvian atrophy, usually on the left side, as a distinctive feature of this disorder. The underlying neuropathology is variable, and can include tau-positive, ubiquitin-positive, TDP43-positive, or Alzheimer's disease (AD) pathology. Genetic biomarkers, such as mutations in progranulin (GRN) and microtubule-associated protein tau (MAPT) genes, have also been found in a subset of patients with PPA (Grossman, 2010). The onset is insidious and highly variable, with cases first occurring in clients in their 20s to 80s; however, the age of onset is usually in the 50s or 60s. Prognosis also varies greatly, with a typical life expectancy of ~7 years post-onset (Forman et al., 2006; Grossman, 2010; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005). PPA is a debilitating condition with no cure that can strike at a relatively early age compared to many neurocognitive disorders. Throughout its progression, patients continue to lose the language skills that they are dependent upon for communicating socially, navigating daily activities, maintaining employment, and functioning independently. Due to the progressive nature of the disorder and the lack of successful intervention options, current treatments for PPA aim to slow the progression of language impairment rather than to ameliorate symptoms; thus, therapy may focus on maintaining functional communication skills at their present levels for the longest time possible (Croot, Nickels, Laurence, & Manning, 2009). There is a great need for research to uncover more successful treatment methods for patients with PPA, in order to combat the isolation and hopelessness they may experience as communication skills deteriorate.

Many interventions in PPA have focused on word retrieval, following from trends in post-stroke aphasia (Croot et al., 2009). More recently, transcranial direct current stimulation (tDCS) has been examined as an adjunct to word retrieval therapy (Tippett, Hillis, & Tsapkini, 2015). It is yet unclear if tDCS-augmented word retrieval interventions improve spoken discourse in PPA. The present study aimed to evaluate the effects of behavioral language therapy in conjunction with transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, on the narrative language abilities of participants with PPA. In the next section, language impairment in PPA will be briefly reviewed. This will be followed by a summary of current intervention methods in PPA, and then a review of studies investigating the potential utility of tDCS intervention for persons with PPA.

Language in PPA

The speech and language abilities of patients with PPA vary based on PPA subtype. Three distinct subtypes of PPA have been established in the literature: nonfluent/agrammatic, semantic, and logopenic (Gorno-Tempini et al., 2011). The nonfluent/agrammatic variant (PPA-G) is characterized by presence of slow, effortful speech with speech sound errors, or grammatical omissions or errors in language production. The semantic variant (PPA-S) is defined by impaired confrontation naming and single-word comprehension. The logopenic variant (PPA-L) presents as impaired sentence and phrase repetition, and impaired single-word retrieval during naming and spontaneous speech (Gorno-Tempini et al., 2011). Additionally, patients can also present with unclassifiable or mixed PPA.

PPA can be diagnosed by investigation of clinical features (e.g., via speech and language testing and analysis), imaging and histopathological findings (e.g., via MRI, DTI, PET, and SPECT), and genetic evidence (Agosta et al., 2015; Ash et al., 2013; Fraser et al., 2014; Gorno-Tempini et al., 2011; Grossman, 2010; Kang et al., 2010; Wilson et al., 2010; Wilson et al., 2009). Speech and language skills assessed may include motor speech production, grammar production, confrontation naming, repetition, language comprehension at the single-word and sentence levels, object and person knowledge, and literacy skills (Gorno-Tempini et al., 2011). Connected speech sample analyses, usually via narrative or picture description tasks, have also provided useful language measures for diagnosing PPA. A recent study investigated the clinical utility of narrative sample analysis in differentiating language in PPA from language in healthy aging and mild cognitive impairment (MCI) (Vander Woude, 2017). The study found that participants with PPA performed worse on specific narrative measures including the proportion of grammatical utterances, rate of speech, number of disfluencies, number of word retrieval errors, and total number of errors in their speech.

Furthermore, narrative analysis and discourse measures have been used to characterize error patterns within the three subtypes of PPA. Research in participants with PPA-G has shown reduced fluency in their narratives, as measured by lower speech rate in words per minute (Ash et al., 2013; Mack et al., 2015; Thompson et al., 2012; Wilson et al., 2010). Participants with PPA-G have also shown deficits in grammatical measures, such as mean length of utterance, proportion of well-formed sentences, and number of dependent clauses per utterance (Ash et al., 2013). Decreased word retrieval abilities and increased speech sound errors have also been found in this subtype (Ash et al., 2006). In PPA-S, studies of connected speech show mixed results with regards to fluency; some studies have shown a reduced speech rate when compared to control participants, while others have shown no significant difference (Ash et al., 2013; Thompson et al., 2012; Wilson et al., 2010). Grammatical deficits, such as reduced MLU and proportion of well-formed sentences, can also be found in this subtype (Ash et al., 2013; Mack et al., 2015; Wilson et al., 2010). Word retrieval abilities are often impacted; studies have found word finding deficits, reduced noun use, and reduced open-class word use (i.e., use of content words) in the narratives of participants with PPA-L (Ash et al., 2013; Ash et al., 2006; Mack et al., 2015; Thompson et al., 2012). Research has also shown fluency deficits in this subtype, including a reduction in speech rate and an increase in disfluencies such as pauses, false starts, and hesitations (Ash et al., 2013; Mack et al., 2015; Thompson et al., 2012; Wilson et al., 2010). Word retrieval deficits, as measured by reduced noun production and greater pronoun production, have also been found in this population (Mack et al., 2015; Wilson et al., 2010). Regarding grammatical measures, participants with PPA-L have shown reduced MLU and reduced proportion of well-formed sentences (Ash et al., 2013; Thompson et al., 2012; Wilson et al., 2010).

Intervention in PPA

As with any neurodegenerative condition, intervention in PPA is challenging due to the heterogenous and progressive nature of the disease. Medications may be used to attempt to treat underlying pathology (e.g., Alzheimer's medications for PPA-L with suspected AD pathology), but evidence of efficacy is lacking (Tippett et al., 2015). Speech-language therapy is a common intervention in this population and often includes impairment-based behavioral language treatment or activity/participation-based treatments (i.e., treatments to improve patients' ability to participate in desired activities or tasks) (Croot et al., 2009). Numerous studies have found benefits from speech-language therapy in primary progressive aphasia, yet evidence of skill maintenance and generalization is inconsistent (Tippett et al., 2015). These trends mirror research in post-stroke aphasia; a meta-analysis of treatment studies documented the efficacy of speech-language therapy, but found generalization of skills to untrained words to be limited (Wisenburn & Mahoney, 2009). In addition, research has shown that while anomia therapy improves single-word retrieval, improvements do not tend to generalize to discourse-level language skills in persons with aphasia, except in retrieval of previously trained words during discourse tasks in some cases (Rider et al., 2008; Peach & Reuter, 2009; Croot et al., 2015). This well-documented lack of generalization highlights the importance of selecting functional, relevant intervention targets when working with people with aphasia in therapy.

More recently, studies using neuromodulation techniques in addition to language therapy have been conducted in participants with PPA (Cotelli et al., 2016; Cotelli et al., 2014; Hung et al., 2017; Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014). One technique, transcranial direct current stimulation (tDCS), will be summarized below, and the research regarding the use of tDCS in PPA intervention will then be reviewed.

Transcranial Direct Current Stimulation in PPA

Transcranial direct current stimulation (tDCS) is a neuromodulation technique that has been studied as a potential treatment option for a multitude of disorders and symptoms, including neurodegenerative conditions (e.g., primary progressive aphasia, dementia, and Parkinson's disease), post-stroke conditions (e.g., motor impairment, aphasia, dysphagia, and neglect), pain syndromes (e.g., fibromyalgia, migraine, and phantom limb syndrome), and psychological disorders (e.g., depression, addiction, and schizophrenia) (tDCS research across populations is summarized in Lefaucheur, 2016). tDCS is a safe, non-invasive, and cost-effective method of neuromodulation, which adds to its potential promise as a widely accessible treatment option in the future (Fridriksson, Hubbard, & Hudspeth, 2012; M. Nitsche et al., 2003). The tDCS process involves applying a small electrical current, usually between 1-2 mA, to the brain via electrodes placed on the scalp. This electrical stimulation is thought to promote an increase in cortical excitability via positively charged anodes, or a decrease in cortical excitability via negatively charged cathodes, by modulating the resting membrane potential of axons in the stimulated region (Nitsche, Liebetanz, Tergau, & Paulus, 2002; Stagg & Nitsche, 2011). Single sessions of tDCS have been shown to produce only temporary changes, and have not generally been found to modulate performance on cognitive or linguistic tasks such as picture naming, verbal fluency, and language learning (Horvath, Forte, & Carter, 2015). Previous research also suggests that the effects of tDCS are task-dependent, and tDCS alone without concurrent task performance or training is not effective in facilitating long-term changes (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Gill, Shah-Basak, & Hamilton, 2015; Rizzo et al., 2014; Terney, Antal,

& Paulus, 2008). However, repetitive tDCS in conjunction with simultaneous therapy or training to utilize the stimulated brain areas might augment functional connectivity in a more sustained way via long-term potentiation or long-term depression (Fridriksson et al., 2012; Miniussi et al., 2008; Monte-Silva et al., 2013; Stagg & Nitsche, 2011).

Many studies have demonstrated that tDCS can transiently improve language functioning in both healthy participants and participants with post-stroke aphasia (Baker, Rorden, & Fridriksson, 2010; Cattaneo, 2011; Fiori, 2011; Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008; Fridriksson, 2011; Fridriksson, Richardson, Baker, & Rorden, 2011; Lefaucheur, 2016; Marangolo et al., 2014; Meinzer, Jähnigen, et al., 2014; Meinzer, Lindenberg, et al., 2014; Monti, 2008; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). However, relatively few have investigated the impact of tDCS on language skills in persons with PPA. A limited number of recent studies have shown improved language skills from tDCS-supplemented language therapy in participants with PPA, with a subset showing preliminary evidence of increased maintenance and generalization of skills (Cotelli et al., 2016; Cotelli et al., 2014; Hung et al., 2017; Tsapkini et al., 2014).

tDCS and Naming Abilities

Many of the studies conducted on tDCS in PPA thus far have examined naming abilities as one outcome measure. A single case study examined the effects of tDCS on language performance in a 67-year old female participant with the agrammatic variant of PPA (Wang, Wu, Chen, Yuan, & Zhang, 2013). The participant received sham stimulation twice daily for 5 days, followed by anodal tDCS twice daily for 5 days, and then the protocol was repeated. No language therapy was administered during stimulation. Electrodes were applied over the left posterior perisylvian region (including Wernicke's area) for each morning session, and over left inferior frontal gyrus (including Broca's area) for each afternoon session. Stimulation or sham stimulation occurred for 20 minutes, with tDCS at 1.2 mA during each session. Subtests from the *Psycholinguistic Assessment in Chinese Aphasia* (PACA) were administered before and after each phase to assess picture naming, auditory word identification, oral word reading, and word repetition performance. Discourse measures were not collected in this study. The authors found no significant changes from baseline after the first round of sham stimulation. After the first round of tDCS stimulation, the participant significantly improved across all four language subtests. However, results must be interpreted with caution, as practice effects could have contributed to the increased performance seen after tDCS.

Another study treated 16 participants with the agrammatic variant of PPA with either tDCS (n=8) or sham stimulation (n=8) in addition to language therapy (Cotelli et al., 2014). For the tDCS group, a current of 2 mA was applied above the dorsolateral prefrontal cortex for 25 minutes per session over 10 sessions in 2 weeks. All participants received Individualized Computerized Anomia Training during treatment sessions to target naming skills. While picture naming accuracy improved significantly with either tDCS or sham stimulation on trained and untrained items for up to 12 weeks, the tDCS-supplemented group performed significantly better than the sham group on treated items as measured immediately after treatment. This increased benefit from tDCS was not maintained at 12 weeks. The authors also found that performance on the naming subtest of the *Aachen Aphasia Test* (AAT) improved only for the tDCS-treated group, and effects were maintained at the 12-week follow-up. Functional communication scales, including the *Stroke and Aphasia Quality of Life Scale* (Hilari, Byng, Lamping, & Smith, 2003) and the *Speech Questionnaire* (Lincoln, 1982) were also completed by the participants and their caregivers, who were blinded to which condition they received (tDCS vs. sham). The authors found significant improvement in perceived benefit for the tDCS group only in self-rated energy level and caregiver-rated speech production, with no maintenance of effects. Together, the data show that application of tDCS during language therapy has the potential to improve outcomes for the agrammatic variant of PPA. These findings were replicated in a follow-up study with the same methods, but without a sham group (Cotelli et al., 2016).

A later study examined the effects of tDCS with concurrent semantic feature analysis therapy (Hung et al., 2017). Four participants with either PPA-L or PPA-S received 20 minutes of 1.5 mA tDCS over 10 sessions. Accuracy in naming trained items improved significantly immediately post-treatment, but performance fell to near baseline after 6 months. Naming accuracy for untrained items did not improve after intervention, and accuracy for trained items declined slower than untrained items. Again, no sham control condition was included in this study, thus the effects of tDCS itself cannot be parsed out.

Two additional studies found no significant change in naming abilities after tDCS treatment, perhaps since language therapy was not administered during stimulation sessions (Gervits et al., 2016; McConathey et al., 2017). Overall, 4/6 studies found that tDCS improved naming abilities; however, the study designs varied in their rigor and most did not include sham conditions. Of the three studies that included language therapy during tDCS stimulation, all showed significantly improved naming abilities. Of the three studies that did not include concurrent therapy, only one single case study showed naming improvement, and this study's results may have been confounded by practice effects. Improvements in naming have been found in agrammatic (Cotelli et al., 2014), semantic, and logopenic (Hung et al., 2017) PPA variants.

tDCS and Spelling Abilities

Rather than word retrieval, one study examined the effects of tDCS on spelling abilities in six participants with agrammatic or logopenic PPA (Tsapkini et al., 2014). The authors used a sham-controlled within-subject crossover design, in which all participants received either tDCS followed by sham stimulation or vice versa. Stimulation was paired with spelling therapy for both tDCS and sham treatment conditions. For the tDCS condition, current between 1-2 mA was applied over the left inferior frontal gyrus (IFG) for 20 minutes per session (15 sessions per condition). Spelling performance on trained and untrained items was measured after each treatment condition, and at 2-week and 2-month follow-up sessions to assess maintenance effects. The authors found that all six participants showed increased abilities after tDCS, and 4/6 showed improvement after sham stimulation. Thus, immediate improvements may have been effects from the spelling intervention itself rather than tDCS. However, tDCS treatment was associated with increased generalization of spelling skills to untrained items, and longer maintenance of skills for both trained and untrained items, compared to sham stimulation. Thus, the study provides evidence that tDCS-supplemented therapy can improve generalization and maintenance of skills in participants with PPA, which are integral components of effective intervention.

tDCS and Narrative Abilities

Of the eight published studies that examined tDCS intervention in PPA, only one study measured narrative language outcomes following intervention (Gervits et al., 2016). Six participants diagnosed with either PPA-G or PPA-L received 20-minutes of tDCS stimulation during 10 sessions over two weeks. Participants engaged in narration of wordless picture books during treatment sessions but did not receive language therapy during tDCS stimulation. Language measures were taken at baseline, immediately after 2 weeks of stimulation, and then during 6-week and 12-week follow-up sessions. Narrative speech samples were elicited using the Cookie Theft picture description task from the *Boston Diagnostic Aphasia Examination* (Goodglass & Kaplan, 1983). The rate of speech (in words per minute) and mean length of utterance were calculated from the narratives and combined into a speech production composite score. The authors found that the composite score improved significantly immediately after treatment, but effects were not maintained at 12 weeks. Results must be interpreted with caution due to the unblinded, uncontrolled study design, which does not provide evidence that improvement can be attributed to tDCS rather than other factors such as the narration task itself or practice effects from repeated neuropsychological testing. Still, the data showing improved narrative language measures in participants with PPA is encouraging, since persons with PPA usually show deterioration of communication skills over time (Libon et al., 2009). Narrative abilities are important for social functioning, as they allow speakers to share their experiences in a cohesive and coherent way during conversation. Elicited narratives can provide a more naturalistic measure of language skills than picture naming or standardized testing, thus increasing ecological validity in assessment. Furthermore, narrative sample analysis can be an efficient tool for clinicians to simultaneously measure multiple language components potentially impacted by PPA and track functional outcomes during intervention. For these reasons, further investigation into the potential effects of tDCS on narrative language skills in PPA is warranted.

Gaps in Knowledge

In summary, research has shown that tDCS can improve a variety of language skills in healthy individuals and persons with post-stroke aphasia (when combined with speech-language therapy). However, only eight studies with varying evidence levels have investigated the use of tDCS to improve language outcomes in primary progressive aphasia (Cotelli et al., 2016; Cotelli et al., 2014; Gervits et al., 2016; Hung et al., 2017; McConathey et al., 2017; Teichmann et al., 2016; Tsapkini et al., 2014; Wang et al., 2013). Due to differences across the study designs, evidence levels, participant characteristics, and outcome measures, more rigorously designed studies are needed to parse out the effects of tDCS on language in this population. Of the eight studies, only one has examined the effects of tDCS on narrative measures in this population to date (Gervits et al., 2016). tDCS has previously been shown to improve discourse-level cohesion in post-stroke aphasia (Marangolo et al., 2014); however, this has not been well investigated in primary progressive aphasia. The present study aimed to address these knowledge gaps by analyzing narratives samples from a diverse group of participants with PPA.

The Present Study

In this retrospective analysis of previously collected narrative samples, the effects of tDCS-augmented anomia therapy were compared to the effects of therapy with sham stimulation to determine if tDCS impacts narrative language abilities in participants with PPA. The pre- and post-tDCS intervention samples were analyzed for discourse measures spanning word retrieval, fluency, and grammaticality. Word retrieval was measured by the total number word retrieval errors (e.g., semantic paraphasias, phonological paraphasias, neologisms, and circumlocutions), Moving Average Type-Token Ratio (MATTR; Covington, 2007), idea density, proportion of pronouns to nouns, and average pause length before nouns and pronouns. Fluency was measured by the average words per minute, total number of disfluencies, and percent of disfluencies in each sample. Grammaticality was measured by the proportion of grammatical utterances, number of utterance-level errors, and the number of verbs per utterance. The total number of errors (word-level errors, utterance-level errors, and disfluencies) was also calculated for each sample. Narrative measures were chosen based on previous research showing sensitivity to language changes in people with aphasia or PPA (Fergadiotis, Wright, & West, 2013; Vander Woude, 2017). If participants with PPA show improved narrative language skills with the addition of tDCS to their treatment, this could have important implications for designing successful interventions for this population and for helping participants regain the discourse-level skills needed for functional communication.

It was hypothesized that tDCS-supplemented therapy would be associated with a reduced number of word retrieval errors when compared to sham stimulation plus therapy. Participants received written and spoken anomia therapy concurrently during tDCS sessions, and trends in aphasia research have shown that directly trained skills and targets are more likely to improve. Conversely, based on previous research showing limited generalization of naming therapy to discourse-level language in aphasia, it was hypothesized that measures of fluency and grammaticality would not improve across either study condition, as anomia therapy does not directly target these skills. While it is possible that measures of fluency would improve along with improved word finding, this might depend on whether the targets trained in therapy were relevant to the narration stimulus. Improvements in fluency measures might be more probable if discourse-level narration tasks were targeted during tDCS-supplemented therapy sessions, as was seen in Gervits et al. (2016). Furthermore, as recent studies have shown that the addition of tDCS to language therapy can improve generalization and maintenance of language skills in participants with PPA, it is worth investigating further to determine whether tDCS can modulate skill generalization in participants with PPA (Cotelli et al., 2016; Tsapkini et al., 2014).

Methods

Participants

The present study was conducted via retrospective analysis of pre-recorded narrative language samples collected from participants with PPA. Narratives from 16 participants across PPA subtypes were analyzed (PPA-G, n=6; PPA-L, n=5; PPA-S, n=5). Participants were enrolled in a clinical trial at Johns Hopkins University, *tDCS Intervention in Primary Progressive Aphasia*, under principal investigator Dr. Kyrana Tspakini (NCT02606422). Participants were referred following diagnosis of PPA by neurologists at Johns Hopkins. Diagnosis and PPA subtype classification were based on data from neuropsychological testing, language testing, MRI, and clinical assessment, and diagnoses were confirmed by study investigators based on discussions of symptomology. All participants were right-handed English-speakers between 50 and 90 years old, who completed at least a 9th grade education. Exclusion criteria were as follows: previous history of stroke or other premorbid neurological disorder; history of language-based learning disorder other than PPA; self-report of uncorrected visual or hearing impairment; inability to follow directions during baseline tasks; or an Aphasia Quotient score of less than 30 on the *Western Aphasia Battery* (WAB; Kertesz, Raven, & PsychCorp, 2007).

Participants had received either tDCS or sham stimulation with concurrent anomia therapy during 15 sessions over three consecutive weeks. A current of 1-2 mA was applied over the left inferior frontal gyrus for 20 minutes during tDCS sessions. Combined written and spoken word production intervention was carried out using a set of pictures of common objects as targets. Participants were prompted to name objects from pictures, repeat the target 30 times, and then write the target. The therapy protocol was adjusted based on individual severity of deficits. For participants with more severe deficits, a set of 10 pictures of common, personally relevant objects were trained during therapy; participants with less severe deficits were trained using a set of 20 low-frequency targets that were not correctly named during baseline assessment.

Levene's test for equality of variances between tDCS and sham groups was not significant for age or education, which indicated equal variance across groups ($\alpha > 0.05$). Independent samples t-tests showed no significant differences between the tDCS and sham groups in age ($p > 0.05$) or education level ($p > 0.05$). Levene's test was significant ($p < 0.05$) for baseline language severity scores between sham and tDCS groups, as measured by the language score of the FTLD-modified Clinical Dementia Rating scale (Knopman et al., 2008). This indicated that equal variance across the groups could not be assumed for this measure. The sham group participants all received a severity rating of 2 on this scale (mean = 2.0, SD = 0), while the tDCS group showed some variance in scores (mean = 1.9, SD = 0.9). A t-test showed no significant difference in language severity across the tDCS and sham groups when equal variance was not assumed ($p > 0.05$).

	Condition	**N**	**Mean**	**Standard Deviation**
Age (years)	sham + therapy	5	74.80	2.86
	tDCS + therapy	11	67.36	8.71
Education (years)	sham + therapy	5	16.40	0.89
	tDCS + therapy	11	16.73	2.72

Table 1: Participant demographics

Narrative Language Sampling

Narrative language samples were elicited from each study participant pre- and post- tDCS or sham plus therapy intervention. The Cookie Theft picture description task from the *Boston Diagnostic Aphasia Examination* was used to elicit the narratives (BDAE; Goodglass & Kaplan, 1983). To collect the narrative samples, participants were shown the Cookie Theft picture stimulus and instructed to relay everything they could about the picture. Responses were audio recorded for later transcription and analysis. The Cookie Theft task has previously been used to assess the effects of tDCS on language functioning in persons with aphasia (Gervits et al., 2016; Norise et al., 2017).

Language Sample Transcription, Coding, and Analysis

Verbatim transcription of the narrative sample audio files was completed in CHAT format using CLAN, an open-source data analysis program that was first created to analyze transcripts in the Child Language Exchange System (CHILDES) database (MacWhinney, 2000). Narrative samples were then manually coded to mark errors and disfluencies for calculation. Codes were retrieved from two resources on the TalkBank website (http://talkbank.org): *Tools for Analyzing Talk Part 2: The CLAN Program* (MacWhinney, 2000) and *A Clinician's Complete Guide to CLAN and PRAAT* (Bernstein Ratner, Brundage, & Fromm, 2018). Error codes and definitions utilized in this study are summarized in Appendix B.

The narrative language samples were analyzed for measures of word retrieval, fluency, and grammaticality primarily using CLAN (MacWhinney, 2000). Language measures were calculated using the EVAL, FREQ, and FLUCALC programs within CLAN. To evaluate word retrieval skills, the FREQ program was used to calculate word retrieval errors (e.g., semantic paraphasias, phonological paraphasias, neologisms, and circumlocutions), MATTR, and the proportion of pronouns to nouns for each sample. The EVAL program was used to calculate the idea density, and the average pause length before nouns and pronouns was calculated manually using Praat (Boersma & Weenik, 2018). To evaluate fluency, the total number and percent of disfluencies in each sample were calculated by the FLUCALC program, and the average rate of speech (in words per minute) was calculated manually. Grammaticality was measured using the EVAL program to calculate the verbs per utterance and total number of utterance-level errors, and the FREQ program to calculate the proportion of grammatical utterances. The total number of errors in each sample was quantified by adding the number of word- and utterance-level errors to the number of disfluencies.

Reliability

Inter-rater reliability was tested to assess agreement in transcription and coding methods between two independent coders. An additional lab member transcribed a random sampling of 12.5% of the narrative language samples in CLAN. The analyst was provided with the original narrative sample audio files and the CLAN error codes list found in Appendix B. When transcription was completed, point-to-point agreement was measured to determine reliability in word transcription and utterance segmentation. Subsequently, the language sample transcripts were compared, and any disagreements were discussed and resolved between the two raters or with assistance from a third rater if agreement could not be reached. After transcription reliability, coding reliability was performed on the same set of samples using point-by-point agreement. Inter-rater reliability (IRR) was found to be high for word transcription (IRR = 94%) and utterance segmentation (IRR = 80%), while coding reliability was fair (IRR = 72%).

Data Analysis

Data analysis was performed using SPSS Statistics Version 24, (IBM Corporation, 2017). Two-way ANOVA tests were performed with time (i.e., pre- vs. post- treatment) and treatment condition (i.e., tDCS vs. sham plus therapy) as the independent factors to determine whether any significant differences in language were found after tDCS intervention. Mann-Whitney U tests were also performed to analyze changes in language measures (T2-T1) between groups with treatment condition as the grouping variable.

Results

Two-way ANOVA tests were performed to determine if any narrative measures changed significantly after tDCS-supplemented therapy vs. sham plus therapy. Levene's test for equality of error variance was not significant for any dependent variable tested ($p > 0.05$), indicating homogeneity of variance across groups. A p-value of 0.01 was used to determine statistical significance in the ANOVA tests. It was found that none of the selected narrative language measures changed significantly after tDCS or sham treatment, and there were no significant differences between the groups (time * condition, $p > 0.01$ for all measures) (Table 2). However, some measures appeared to show a pattern of decline in performance in the sham plus therapy group compared to stable performance in the tDCS plus therapy group, including: total number of disfluencies, percent disfluencies, proportion of grammatical utterances, verbs per utterance, number of utterance-level errors, and total number of errors. These findings are summarized in

Figures 1-6. Although visual inspection of the patterns suggested a decline in the sham group, the p-values of all these comparisons exceeded 0.1.

	Language Measure	**Pre-sham + therapy (T1)**	**Post-sham + therapy (T2)**	**Pre-tDCS + therapy (T1)**	**Post-tDCS + therapy (T2)**
Word Retrieval	MATTR	0.82 (0.05)	0.80 (0.03)	0.83 (0.06)	0.81 (0.07)
	Idea density	0.42 (0.07)	0.43 (0.08)	0.41 (0.06)	0.42 (0.05)
	Proportion pronouns to nouns	0.50 (0.21)	0.48 (0.20)	0.41 (0.23)	0.41 (0.26)
	Avg. pause length before nouns and pronouns	0.43 (0.37)	0.35 (0.23)	0.47 (0.38)	0.58 (0.72)
	Total number of word retrieval errors	2.00 (2.35)	2.40 (1.82)	2.45 (2.81)	2.64 (2.38)
Fluency	Total number of disfluencies	20.20 (8.73)	34.80 (22.83)	26.36 (23.55)	27.55 (17.19)
	Percent disfluencies	0.37 (0.21)	0.48 (0.36)	0.36 (0.27)	0.36 (0.21)
	Average words per minute	78.58 (29.23)	75.89 (31.33)	75.20 (29.58)	77.19 (35.17)
Grammaticality	Proportion grammatical utterances	0.47 (0.32)	0.43 (0.29)	0.52 (0.31)	0.61 (0.28)
	Verbs per utterance	1.65 (0.58)	1.27 (0.47)	1.36 (0.44)	1.37 (0.52)
	Number of utterance-level errors	4.20 (2.78)	6.40 (3.85)	4.36 (2.20)	4.27 (3.41)
Overall	Total number of errors	26.60 (12.10)	43.80 (27.15)	33.00 (24.42)	34.27 (18.83)

Table 2: Mean narrative measures pre- and post-tDCS plus therapy or sham plus therapy

a. Mean (SD)

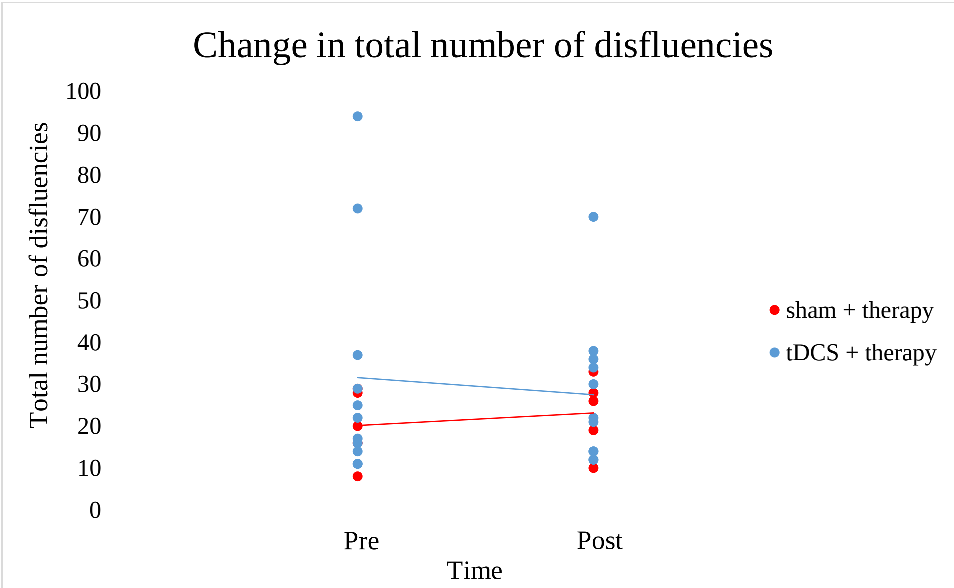


Figure 1: Change in total number of disfluencies in sham plus therapy vs. tDCS plus therapy groups

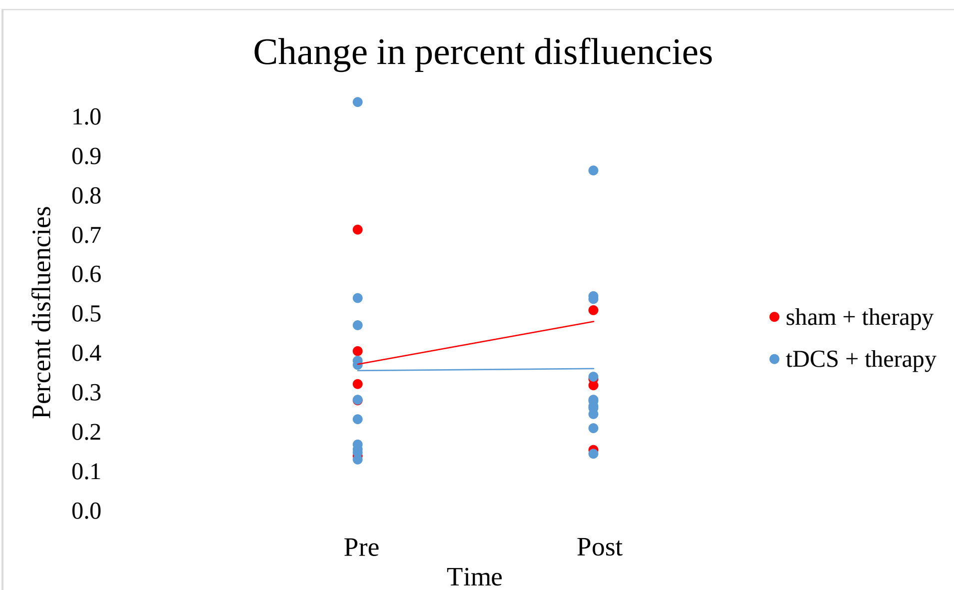


Figure 2: Change in percent disfluencies in sham plus therapy vs. tDCS plus therapy groups

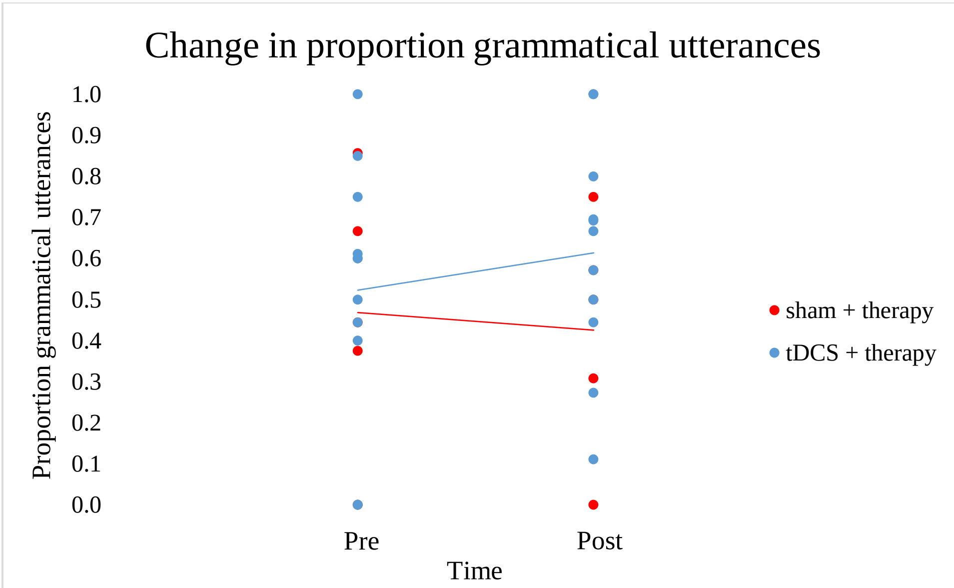


Figure 3: Change in proportion of grammatical utterances in sham plus therapy vs. tDCS plus therapy groups

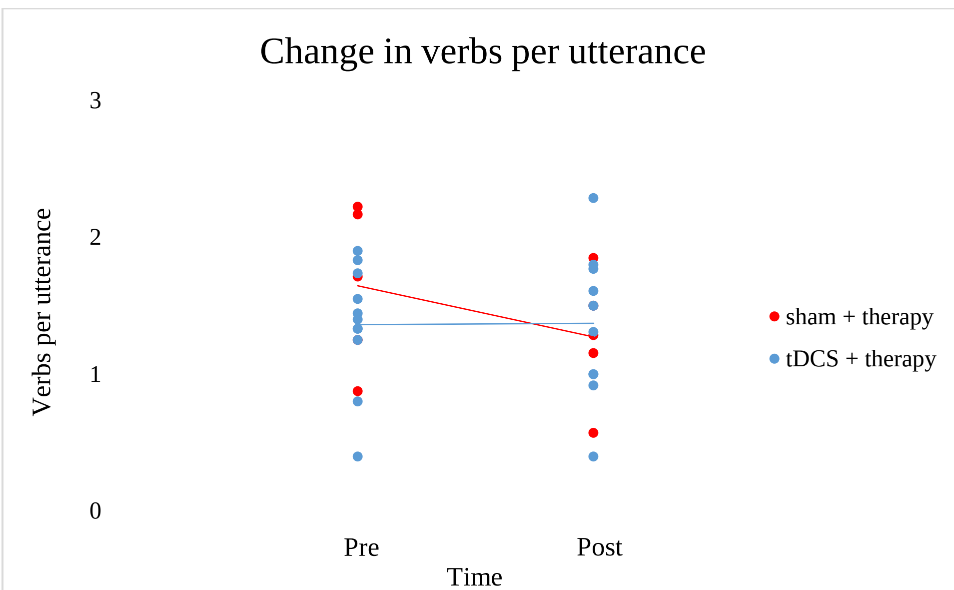


Figure 4: Change in verbs per utterance in sham plus therapy vs. tDCS plus therapy groups

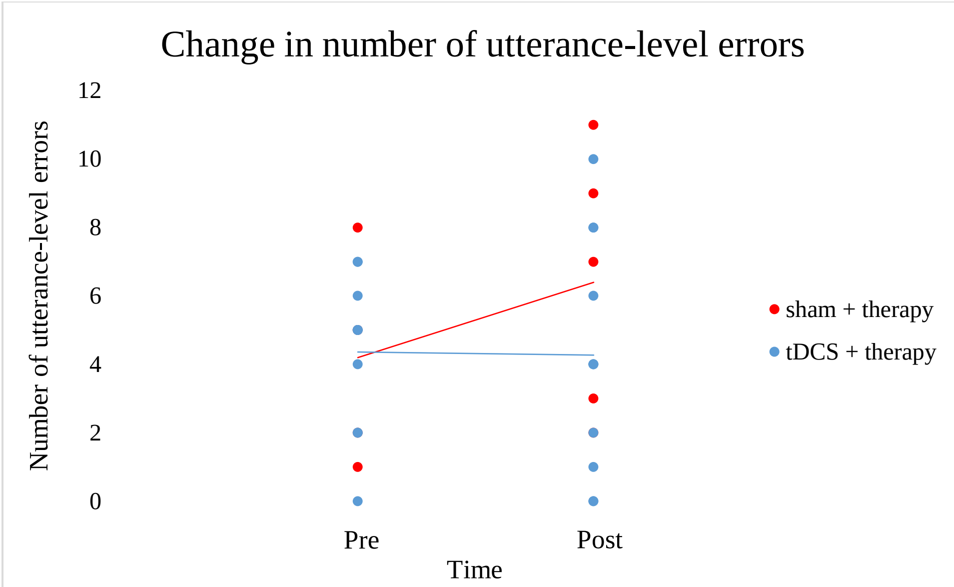


Figure 5: Change in total number of utterance-level errors in sham plus therapy vs. tDCS plus therapy groups

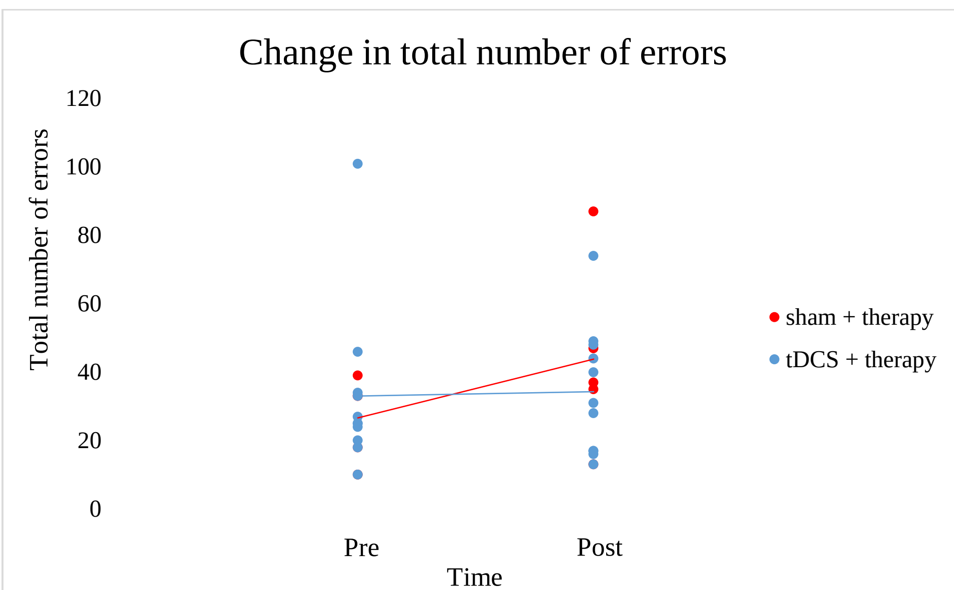


Figure 6: Change in total number of errors in sham plus therapy vs. tDCS plus therapy groups

Results from the Mann-Whitney U tests are summarized in Table 3. Due to the large number of variables tested, a p-value of 0.01 was used to determine significance in order to reduce the chance for Type I errors. No variables were significant at $p < 0.01$, indicating no group differences in changes in language measures (T2-T1) between the tDCS plus therapy and sham plus therapy groups. However, one variable approached significance at $p < 0.05$ (change in verbs per utterance). For this measure, the sum of ranks for the tDCS plus therapy group ($\Sigma R_2 = 113$) was larger than that of the sham plus therapy group ($\Sigma R_1 = 23$), indicating better performance in the tDCS plus therapy group (i.e., a higher average number of verbs per utterance measure after intervention).

Language Measure (T2 – T1)	**Mann-Whitney U**	**Wilcoxon W**	**Z**	**Asymp. Sig. (2-tailed)**
MATTR	25	40	-.28	.78
Idea density	24.5	90.5	-.34	.73
Proportion pronouns to nouns	23	38	-.51	.61
Avg. pause length before nouns and pronouns	27	42	-.06	.96
Total number of word retrieval errors	27	42	-.06	.95
Total number of disfluencies	13.5	79.5	-1.59	.11
Percent disfluencies	19	85	-.96	.37
Average words per minute	24	39	-.40	.69
Proportion grammatical utterances	17	32	-1.19	.23
Verbs per utterance	8	23	-2.2	.03
Number of utterance-level errors	15	81	-1.43	.15
Total number of errors	14.5	80.5	-1.48	.14

Table 3: Mann-Whitney U test results

Discussion

The present study aimed to evaluate whether tDCS-supplemented language therapy improved narrative language abilities in participants with primary progressive aphasia versus sham stimulation with therapy. Results and potential clinical implications will be summarized in the following sections, and limitations of the study and future research directions will then be reviewed.

tDCS and Narrative Abilities

Statistically significant differences were not found between the sham and tDCS treatment groups for any narrative language measure tested. Thus, tDCS-supplemented anomia therapy was not associated with changes in narrative language ability. While it was hypothesized that changes in word retrieval measures would be found after tDCS intervention, the results of this study are consistent with the literature, which has frequently found a lack of generalization of trained skills to novel tasks or targets in primary progressive aphasia (Tippett et al., 2015; Croot et al., 2009). Results are also consistent with findings of limited skill generalization from single word-retrieval therapy to untrained targets and to discourse-level language skills in post-stroke aphasia (Wisenburn & Mahoney, 2009; Rider et al., 2008).

Anomia therapy generally targets single word retrieval, which is a common deficit in PPA (Gorno-Tempini et al., 2011). Word retrieval is achieved via complex neural mechanisms, while narration, in addition to utilizing networks for word retrieval, necessitates use of language skills across all domains (i.e., phonology, morphology, syntax, semantics, and pragmatics) (Berko Gleason, 2005). Word retrieval and subsequent production are carried out via the following processes: conceptual preparation, lemma retrieval, lemma selection, phonological code retrieval, syllabification, phonetic encoding, and articulation (Indefrey, 2011; Indefrey & Levelt, 2004). Narration necessarily involves word retrieval, as well as processing and production of microlinguistic elements (i.e., within-sentence elements, such as lexical, syntactic, and semantic features at the word- and sentence-levels) and macrolinguistic elements (e.g., between-sentence elements, such as cohesion, coherence, and discourse grammar) (Brownell, 1988). Narration also recruits cognitive and socio-emotional networks for memory encoding and retrieval, theory of mind, and emotional regulation, and personal storytelling involves temporal organization of experiences, narrative evaluations, and attention to social cues (Gola et al., 2015).

Perhaps due to the complex and dynamic nature of systems interactions for narration, narrative skills can be difficult to improve via word retrieval therapy in patients with aphasia and PPA. Improving narratives can be especially trying if therapy does not directly target discourse-level language skills, since generalization of naming therapy to discourse has been shown to be limited in aphasia (Rider et al., 2008; Peach & Reuter, 2009; Croot et al., 2015). Single word-retrieval therapy may not necessarily target the higher-level language skills needed to produce a cohesive and coherent narrative. According to principles of experience-dependent neuroplasticity, the specific neurological networks used for narration should be trained in therapy in order to maintain and reinforce relevant neurological pathways (Kleim & Jones, 2008).

Participants in the present study received written and spoken anomia therapy during 15 stimulation sessions over three weeks. Thus, measures of naming skills (vs. narrative skills) may have been more likely to show improvement with tDCS-supplemented therapy, especially if targets trained in therapy were included in the analysis. This would be consistent with previous research showing improved naming of trained items after word-retrieval therapy in aphasia, and limited improvement for untrained items (Wisenburn & Mahoney, 2009). Furthermore, generalization of skills from word-retrieval therapy to discourse-level tasks has not been consistently demonstrated in the aphasia literature, especially for untrained words (Rider et al., 2008; Peach & Reuter, 2009; Croot et al., 2015). As a limited set of 10-20 targets was trained in the current study, it may have been unlikely that trained words were naturally elicited by the Cookie Theft picture description task. If trained words were not often retrieved during narration, this may have contributed to the lack of change in narrative measures post-intervention.

Numerous studies have demonstrated that utilization of underlying brain networks via task practice during stimulation is critical for tDCS-mediated skill improvement (Gill et al., 2015; Rizzo et al., 2014; Andrews et al., 2011; Terney et al., 2008). It is possible that narrative language measures did not improve in the current study since narration was not practiced and thus relevant language networks were not activated during stimulation. It might have been beneficial for participants to engage in narration tasks during stimulation to utilize brain regions relevant to narrative production specifically. For example, participants in a study by Gervits et al. (2016) narrated wordless picture books during tDCS sessions and were found to have improved composite language scores as measured from narratives. Furthermore, some researchers have demonstrated improvements in narrative language measures in aphasia when word-retrieval therapy was carried out via discourse-based approaches, for example, in group therapy

(Antonucci, 2009; Peach & Reuter, 2009; Falconer & Antonucci, 2011). It may be worthwhile for future studies to focus on discourse, conversation, or narrative-based therapy approaches during tDCS sessions to see if these methods are associated with improvements in narrative language and functional communication skills in persons with PPA.

It is possible that the time frame of the study was too short to see significant changes in narrative measures post-intervention. The time elapsed between T1 to T2 was approximately three weeks for each participant; this may not have been enough time for the intervention to promote changes in narrative measures, especially if narrative measures were not directly trained during therapy. Additionally, follow-up testing sessions would be helpful to include in future studies to determine if tDCS can promote increased maintenance of skills. In a previous study of tDCS in PPA, while both sham and tDCS-supplemented therapy groups showed significant improvement in spelling of trained items immediately after treatment, only the tDCS group tended to maintain benefits at 2-week and 2-month follow-up assessments (Tsapkini et al., 2014). Further studies to replicate these results will be an important next step in PPA research. To assess the longer-term utility of tDCS intervention in this population, studies that continue therapy for longer than three weeks may be another important research area, as tDCS is thought to be able to promote neuroplastic changes via long-term potentiation or long-term depression with repeated administration (Miniussi et al., 2008; Stagg & Nitsche, 2011; Fridriksson et al., 2012).

While no changes in narrative language measures were found to be significant in the current study, some general patterns found in the data were highlighted. The mean number of disfluencies, percent of disfluencies, number of utterance-level errors, and total number of errors in the samples tended to increase in the sham plus therapy group from T1 to T2, while remaining relatively stable in the tDCS plus therapy group. Similarly, the mean proportion of grammatical utterances and number of verbs per utterance tended to decline in the sham group, while remaining stable in the tDCS group. Since these changes in narrative language measures were not statistically significant, additional research is needed to see if the patterns can be replicated and to determine whether they could reach statistical significance, perhaps in a larger sample size. These patterns showing increasing error rates over time in the sham group are consistent with the assumption that skills will continue to decline in PPA due to the degenerative nature of the disorder (Mesulam, 2001). It is possible that tDCS, when combined with speech-language therapy, may slow this decline and improve maintenance of skills trained in therapy. While the current study is not conclusive, other recent studies have provided preliminary evidence for increased generalization and maintenance of language skills with tDCS-supplemented language therapy (Cotelli et al., 2016; Cotelli et al., 2014; Hung et al., 2017; Tsapkini et al., 2014). Future studies aiming to replicate and expand on these patterns to significance are necessary to evaluate the value of tDCS as an adjunct to therapy for patients with PPA.

Limitations and Future Research Directions

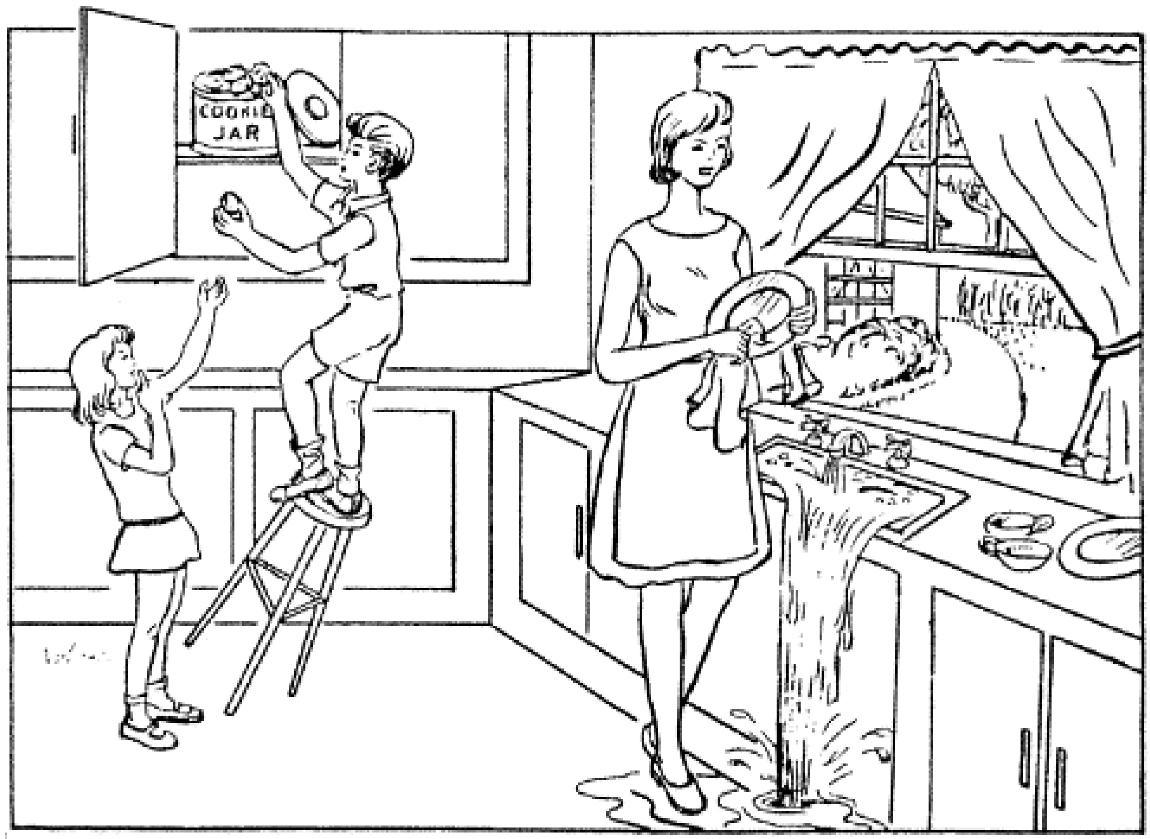
One major limitation of the present study was the small and unbalanced sample size. There was high variability in skills and deficits across the 16 participants, and only five participants received the sham condition. Future studies with larger populations and more equal representation across the experimental groups will be helpful in determining the effects of tDCS on narrative language abilities. Furthermore, including a control group that received no treatment at all may have been helpful for comparison to the sham and tDCS groups. All participants in the study received concurrent language therapy with tDCS or sham stimulation, and it is possible that participants may have declined more without any intervention. Another limitation was the length of the narrative samples that were analyzed. The Cookie Theft picture description is a very short narrative task; some samples contained as little as four utterances and were less than one minute in length. The selected language measures may not have been sensitive enough to capture subtle changes in narrative abilities in such short samples. Additional studies analyzing longer narrative samples would be helpful to understand whether tDCS-supplemented therapy can improve narrative skills in this population. Future studies using more varied and personally-relevant narrative elicitation tasks may also help participants produce longer, more naturalistic samples.

Another limitation of this study is that narrative skills were not directly trained during the tDCS-augmented therapy sessions, and patients with PPA have previously shown difficulty with generalization of skills learned in therapy. Furthermore, tDCS research has generally shown better outcomes when target tasks are practiced during stimulation. Results may have been more promising if participants engaged in narrative practice during therapy sessions, as this would have targeted discourse-level skills more directly. Additionally, data on anomia treatment outcomes were not available to analyze for this study (i.e., change in naming scores pre- and post-intervention). This limited the ability to assess whether generalization occurred from the anomia therapy to narrative outcomes. A multiple baseline study design may have been helpful to gauge individual participants' language skill deterioration before therapy was administered. Measuring the natural rate of decline in narrative language skills prior to treatment would allow researchers to control for this rate and see if it has an effect on treatment outcomes. Analysis of data collected at various time points post-intervention would additionally allow for examination of potential effects of tDCS on narrative language skill maintenance, which would be an important outcome for successful intervention in PPA.

In summary, narrative language measures were not found to significantly change with tDCS-supplemented anomia therapy versus sham stimulation plus therapy in this study. Future studies analyzing longer narrative samples from a greater number of participants may help to further elucidate the effects of tDCS on narrative abilities, including effects on generalization and maintenance of skills. Additional research can examine the effects of increasing the number of tDCS-supplemented therapy sessions to determine potential for neuroplastic changes in this population, as well as the addition of targeted narration task practice to utilize relevant brain networks during stimulation.

Appendices:

Appendix A: Image from Cookie Theft Picture Description Task from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983)



Appendix B: CLAN Transcription Error Codes

Codes and definitions were adapted from:

Tools for Analyzing Talk Part 2: The CLAN Program (MacWhinney, 2000).
Retrieved from: https://talkbank.org/manuals/CLAN.pdf

A Clinician's Complete Guide to CLAN and PRAAT (Bernstein Ratner, Brundage, & Fromm, 2018).
Retrieved from: https://talkbank.org/manuals/Clin-CLAN.pdf

Connected language in primary progressive aphasia: testing the utility of linguistic measures in differentially diagnosing PPA and its variants (Van der Woude, 2017).

Word Retrieval Error Codes

Phonological paraphasia: [* p]

- Definition: For one-syllable words with an onset (initial phoneme/phonemes) and a vowel nucleus plus coda (final phoneme or phonemes), the error must match on 2 out of 3 of those elements. The part of the syllable with an error may be a substitution, addition, or omission. For multi-syllabic words, the error must have complete syllable matches on all but one syllable, and the syllable with an error must meet the one-syllable word match criteria previously mentioned.
- Example: soon [* p] (if participant said "soon" for "noon")

Semantic paraphasia: [* s]

- Definition: A word that is related in meaning to the target word is used in place of the target word.
- Example: rake [* s] (if participant said "rake" for "shovel")

Neologism: [* n]

- Definition: Non-words that do not meet the criteria for phonological or semantic errors.
- Example**:** kargiv [* n]

Circumlocution: [+ cir]

- Definition: When the participant talks around words or concepts.
- Example: and then she got her, you know, that thing with the hole in it, the container, I mean, I don't know, but she brought it to work . [+ cir]

Unintelligible speech: xxx

Fluency Error Codes

Pause: (.)

- Definition: Pauses that last longer than one second. This symbol isn't needed if the pause occurs between utterances.
- Example: it's a (.) bat

Filled Pause: **&-**

- Definition: A pause filled with a word. The word used should be considered a disfluency, as opposed to a word that has communicative function
- Examples: &-um, &-like, &-you_know (multi-word fillers are connected with an underscore)

Prolongation: : (colon after sound that is prolonged)

- Definition: Stretching out a sound or syllabic element.
- Example: s:top

Phonological fragment: &+

- Definition: Fragments of a word prior to the start of the target word. The same fragment is not repeated more than twice (if it is, use "repeated segments" code instead).
- Example: I &+v went to the store.

Repeated segment: ↫

- Definition: A segment of the word is repeated more than twice. This can occur at the beginning of a word or at the end of a word. If at the beginning of the word, unlike a phonological fragment, the sound is repeated more than once. To create arrow, hold "F2" and "/". Iterations inside of the sequence are marked with hyphens.
- Example: ↫r-r-r↫rail or jump↫ump↫

Word repetition: [/]

- Definition: A whole word is repeated once.
- Example: jam [/] jam

Multiple whole word repetition: [x N] (indicate number of repetitions in place of "N")

- Definition: A whole word is repeated more than once.
- Example: cookie [x 5]

Phrase repetition: <>[/]

- Definition: When the speaker repeats a phrase within a sentence without changing it at all.
- Example: <here we> [/] here we are.

Phrase revision: <>[//]

- Definition: When the speaker changes something (usually syntax) in an utterance but maintains the same idea.
- Example: <I want to> [//] let's go to the mall.

Grammatical Error Codes

Grammatical error: [+ gram]

- Definition: Utterances in which necessary grammatical elements (e.g., subjects, verbs, auxiliaries, prepositions) are missing or incorrectly used, with the exception of appropriate one-word answers to questions or to other appropriate one-word communicators (e.g., yes, mhm). Also refers to utterances with errors in word order, syntax, or grammatical morphology.
- Example: they were going on for and they aren't yet going too. [+ gram]

Appendix C: Secondary Analysis of Individual Factors to Predict tDCS Narrative Language Outcomes in PPA

Recently, researchers have begun to assess individual factors that may modulate language improvement in persons with PPA who undergo tDCS intervention. Evidence from this research area can help determine whether participants with certain profiles are more likely to benefit from tDCS treatment. The present study originally aimed to analyze individual factors that predicted more positive outcomes with tDCS-supplemented therapy. This analysis was not included in the main study due to the limited sample size; however, results are summarized below.

Two previous studies have investigated individual factors that may influence outcomes from tDCS in participants with PPA. A study by McConathey et al. (2017) investigated the potential impact of baseline language abilities on tDCS-mediated language improvement. The authors recruited 7 participants with PPA-G and PPA-L for a blinded, sham-controlled crossover study. Participants received either tDCS or sham stimulation for 20 minutes, in 10 sessions over two weeks. Anodal stimulation was placed over the left prefrontal region, and cathodal stimulation over the left occipital region. The authors found that participants with lower baseline language scores generally showed greater improvement from tDCS treatment than high-performing participants, which is consistent with the results of a previous study of tDCS in post-stroke aphasia (Norise, Sacchetti, & Hamilton, 2017). Thus, the authors suggest that tDCS treatment may be more beneficial for PPA participants at later stages of disease progression, when language skills are more compromised. While other studies have similarly found greater benefits from tDCS in lower-performing healthy participants (Looi et al., 2016;

Turkeltaub et al., 2012), further research is necessary in larger and more diverse participant samples to determine if a critical window for tDCS treatment exists for clients with PPA.

Another study of 18 participants with PPA-G examined the predictive value of grey matter density in improvement in naming abilities with tDCS treatment (Cotelli et al., 2016). Participants received 10, 25-minute sessions of anodal tDCS over the left dorsolateral prefrontal cortex over two weeks, while simultaneously participating in language therapy (Individualized Computerized Anomia Training; Cotelli, 2014). The authors measured grey matter density using MRI images and voxel-based morphometry and found positive correlations between baseline grey matter density and improvement in naming performance after therapy with tDCS treatment. Specifically, greater grey matter density in the left fusiform gyrus, left middle temporal gyrus, and right inferior temporal gyrus was correlated with greater improvement in object naming, while grey matter density in the left middle temporal gyrus was associated with greater improvement in action naming. The authors suggest that earlier intervention with tDCS, when there is less atrophy, may be more beneficial for participants with the agrammatic variant of PPA. This interpretation conflicts with that put forth in the previously mentioned study by McConathey et al. (2017), but is more consistent with current research findings in which the benefits of earlier intervention have been documented in this population across various intervention methods (Tippett et al., 2015). However, the investigators only examined participants with PPA-G, thus results may not generalize to other subtypes.

PPA subtype may also be an individual factor that affects outcomes with tDCS intervention due to differences in language deficits, underlying pathology, and atrophy patterns across subtypes (Grossman, 2010). Of the eight studies summarized thus far, four examined tDCS effects in a homogenous sample of participants with the same PPA subtype (Cotelli et al., 2016; Cotelli et al., 2014; Teichmann et al., 2016; Wang et al., 2013). Four studies examined two PPA subtypes in their samples, but between-group differences were not reported (Gervits et al., 2016; Hung et al., 2017; McConathey et al., 2017; Tsapkini et al., 2014). No tDCS studies thus far were found to compare participants across all three PPA subtypes in their analyses.

The research evidence describing individual factors that may predict more successful tDCS treatment in participants with PPA is currently very limited. This secondary analysis sought to determine whether PPA subtype, baseline language performance, or baseline cognitive skills may account for any effects of tDCS on narrative abilities. PPA subtype was chosen as a variable due to the substantial differences in underlying pathology and symptomology across variants, which may contribute to differing responses to tDCS intervention. Baseline language measures, including *Boston Naming Test* scores (Kaplan, Goodglass, & Weintraub, 1983), semantic fluency, and phonological fluency performance, were selected for analysis as they have previously been shown to affect tDCS-mediated outcomes in PPA and post-stroke aphasia. Cognitive measures were chosen due to the well-studied link between cognition and language. Specifically, working memory (as measured by forward and backward digit span performance) was analyzed due to its importance in mediating language learning and processing.

Regarding PPA subtype, there is not enough evidence to predict whether certain subtypes of PPA may be more likely to benefit from tDCS-supplemented therapy. Based on the characteristics of impairment in each subtype, it was hypothesized that participants with PPA-L may be more likely to benefit from tDCS intervention, as the concurrent anomia therapy directly targeted one of the most prominent deficits in this subtype (word-finding). Regarding baseline language performance, it was hypothesized that lower baseline naming abilities would be associated with increased benefit from tDCS, as measured by changes in narrative language measures. This result would be consistent with previous studies showing increased benefit from tDCS when baseline language skills were lower (McConathey et al., 2017; Norise et al., 2017). As working memory, particularly the phonological loop, is important for language learning and processing, it was predicted that participants with greater baseline working memory skills may show greater improvement from tDCS-supplemented therapy.

Data Analysis

To examine if tDCS effects differ based on individual factors, participant data was analyzed via multiple regressions in SPSS. Individual characteristics (i.e., PPA subtype, baseline language task performance, and baseline cognitive task performance) were included as independent variables, while changes in selected discourse measures (T2-T1) were calculated and included as dependent variables. Separate regressions were run for each discourse measure. To minimize the potential for type I errors, given the multiple number of regressions that were conducted, a more conservative p-value of 0.01 was used.

Results

Models that achieved statistical significance ($p < 0.01$) are summarized in Tables 3 and 4. Significant models were found for the following dependent variables: change in number of disfluencies ($R^2 = .89$, $F(7, 8) = 9.1$, $p < 0.01$) and change in total number of errors ($R^2 = .88$, $F(7, 8) = 8.29$, $p < 0.01$).

In Regression Model 1 (Table 4), the dependent variable was the change in mean number of disfluencies in the samples from T1 to T2. Participants' baseline semantic fluency and phonological fluency scores significantly contributed to Model 1 ($p < 0.001$ for both measures). Semantic fluency had a significant negative regression weight, indicating that participants with higher baseline performance on this test were expected to have a greater reduction in disfluencies after controlling for the other variables in the model. Conversely, results demonstrated that participants with higher baseline phonological fluency scores were expected to show an increase in number of disfluencies after treatment when other variables were accounted for.

Variable	Correlation with change in number of disfluencies	Unstandardized coefficients (b)	Standardized coefficients (β)
Treatment condition ^	-0.46	-21.08	-0.72
PPA variant #	0.27	4.14	0.25
Boston Naming Test score	-0.20	1.30	0.99
Semantic fluency score	-0.34	-2.16 **	-2.04
Phonological fluency score	-0.12	2.48 **	1.82
Digit span forward	-0.03	-1.98	-0.25
Digit span backward	-0.36	-5.30	-0.59

Table 4: Results from Regression Model 1 - Predictors of change in number of disfluencies

a. Dependent Variable: Change in number of disfluencies from T1 to T2
b. ^ coded as 0=sham and 1=tDCS
c. # coded as 1=nonfluent 2=logopenic and 3=semantic
d. * $p < 0.01$ ** $p < 0.001$
e. Model summary: $R^2 = .89$, $F(7, 8) = 9.1$, $p < 0.01$

Regression Model 2 shows expected change in the mean total number of errors in the samples based on predictor variables (Table 5). Coefficients were similar in weight and significance to those in Model 1, since the total number of errors was calculated to include the number of disfluencies. The number of disfluencies in the samples tended to be considerably large compared to the number of other errors, and thus the data was skewed toward those values. Again, a significant negative regression weight was found for semantic fluency scores ($p < 0.01$), while a significant positive weight was found for phonological fluency scores ($p < 0.001$). Thus, higher semantic fluency performance was associated with a reduction in errors, while higher phonological fluency was associated with an increase in errors.

Variable	**Correlation with change in total number of errors**	**Unstandardized coefficients (b)**	**Standardized coefficients (β)**
Treatment condition ^	-0.46	-26.05	-0.75
PPA variant #	0.26	5.43	0.28
Boston Naming Test score	-0.17	1.52	0.98
Semantic fluency score	-0.29	-2.51 *	-2.01
Phonological fluency score	-0.07	3.03 **	1.88
Digit span forward	-0.03	-3.05	-0.33
Digit span backward	-0.33	-5.78	-0.55

Table 5: Results from Regression Model 2 - Predictors of change in total number of errors

a. Dependent Variable: Change in total number of errors from T1 to T2
b. ^ coded as 0=sham and 1=tDCS
c. # coded as 1=nonfluent 2=logopenic and 3=semantic
d. * $p < 0.01$ ** $p < 0.001$
e. Model summary: $R^2 = .88$, $F(7, 8) = 8.29$, $p < 0.01$

Discussion

Two significant multiple regression models were identified using treatment condition, PPA subtype, baseline language test scores, and baseline cognitive test scores as predictors of change in narrative language measures. Significant coefficients were found for two linguistic predictors: baseline semantic fluency and phonological fluency scores. Results suggested that higher baseline semantic fluency and lower baseline phonological fluency scores were associated with expected decreases in errors and disfluencies (i.e., improved outcomes) in narrative language post-intervention. It was hypothesized that lower baseline linguistic measures would predict increased benefit from tDCS-supplemented language therapy, as had been found in previous studies demonstrating improved tDCS-mediated outcomes with lower language skills in post-stroke aphasia and PPA (Norise, Sacchetti, & Hamilton, 2017; McConathey, 2017). Analyses did not reveal differences in narrative outcomes between sham and tDCS groups, so any effects from tDCS itself could not be determined from this study. However, the positive phonological fluency coefficient appeared to support the hypothesis that lower baseline linguistic skills may be associated with better narrative language outcomes after intervention (regardless of sham vs. tDCS treatment condition).

It is difficult to draw general conclusions about the predictive value of baseline language functioning from this study since the effects of baseline semantic fluency and phonological fluency on narrative outcomes were contradictory. This may be partially explained by research showing that semantic and phonological fluency rely on different neural networks; neural correlates for semantic fluency have been found in the temporal lobe, while correlates for phonological fluency have been found in the frontal lobe (Baldo, Schwartz, Wilkins, & Dronkers, 2006; 2010; Chapados & Petrides, 2013). A recent study reported a double dissociation between the two measures in persons with aphasia, and suggested involvement of left frontal areas in phonological fluency and left temporal areas in semantic fluency performance (Baldo et al., 2010). Another recent study, which examined generalization patterns in aphasia, found that participants with relatively stronger semantic processing and relatively weaker phonological output processing showed improved generalization in naming untrained items, regardless of aphasia subtype (Best et al., 2013). This finding is supported by the results of the current study, which also suggest that higher semantic and lower phonological task performance may be associated with improved therapy outcomes in PPA. Further research is needed to examine the potential predictive value of baseline semantic and phonological fluency scores for narrative language outcomes in PPA. If these results can be replicated in larger participant samples, semantic and phonological fluency testing could provide clinicians with a straightforward way to gauge potential for improving language outcomes and skill generalization in PPA intervention.

Significant coefficients were not found for PPA subtype or baseline cognitive measures in this limited study. It is possible that selecting different baseline cognitive and linguistic measures might have produced more significant results, or that the lack of changes in narrative measures generally limited the regression analyses. Previous studies in language development and related fields have identified other individual factors that predict later narrative abilities and thus may be worth investigating in future studies in participants with PPA. One study of early language development found that children who used gestures to represent characters' viewpoints during story retell were more likely to produce better-structured narratives in later years (Demir, Levine, & Goldin-Meadow, 2015). Another study found that parental use of decontextualized language with 30-month-old children predicted better narrative language outcomes in kindergarten (Demir et al., 2015). A recent study of healthy younger and older adults found that attention, working memory, and episodic memory abilities contributed to discourse comprehension and production for the older adult group only (70-89 years old) (Wright et al., 2011). Cognitive measures analyzed in the study included: the Wechsler Memory Scale—Third Edition (Wechsler, 1997); the Comprehensive Trail Making Test (Reynolds, 2002); and the Stroop Color and Word Test (Golden, 2002). In contrast, the cognitive measures selected for the present study (i.e., forward and backward digit span) did not show significant association with change in narrative language outcomes. It is possible that the measures chosen in Wright et al., (2011) were more appropriate for determining the influence of cognition on narrative skills, or that the healthy participants differed from those with PPA. Future research into narrative abilities in PPA post-tDCS should examine a wider range of cognitive measures as potential predictors of change in language outcomes.

Additional studies have shown that altering the narrative stimulus or task instructions can affect the quality of narratives produced in various populations (Wright & Capilouto, 2009; Demir et al., 2014). For example, one study found that children produced better narratives when prompted to retell a story presented in video format with co-speech gestures during narration (Demir et al., 2014). The authors suggested that including co-speech gestures in narrative prompts may help provide scaffolding for teaching and improving narrative skills. Another study found that requesting temporal-causal information during picture description task instructions helped participants with aphasia convey temporal-causal relationships and improve narrative language measures (Wright & Capilouto, 2009). Thus, prompting participants to tell stories that have a beginning, middle, and end when eliciting narratives, rather than asking them to simply describe the picture, may be helpful for some persons with aphasia to produce richer narratives. Research in this area highlights the importance of comprehensive assessment of narrative abilities to get a true picture of participants' skills, and continued research in this field can help persons with aphasia and their communication partners learn strategies to improve their daily interactions, activity participation, and quality of life. Overall, the aforementioned factors (i.e., gesture use, communication partner's use of decontextualized language, memory, attention, narrative stimulus type, and task instructions) can be explored further to gauge their potential predictive value for tDCS-supplemented narrative language outcomes in PPA.

In summary, multiple regression analyses identified two individual factors that may predict differences in outcomes after language therapy or tDCS-supplemented therapy in patients with PPA: baseline semantic fluency and phonological fluency scores. However, results must be interpreted with caution due to the small sample size. Research in larger participant pools will be necessary to identify individual factors that may predict more positive tDCS-mediated therapy outcomes.

References:

Agosta, F., Ferraro, P., Canu, E., Copetti, M., Galantucci, S., Magnani, G., . . . Filippi, M. (2015). Differentiation between Subtypes of Primary Progressive Aphasia by Using Cortical Thickness and Diffusion-Tensor MR Imaging Measures. *Radiology, 276*(1), 219-227.

Andrews, S., Hoy, K., Enticott, P., Daskalakis, Z., & Fitzgerald, P. (2011). Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. *Brain Stimul, 4*(2), 84-89. doi: 10.1016/j.brs.2010.06.004

Antonucci, S. (2009). Use of semantic feature analysis in group aphasia treatment. *Aphasiology,* 23(7–8): 854–866.

Ash, S., Evans, E., O'Shea, J., Powers, J., Boller, A., Weinberg, D., . . . Grossman, M. (2013). Differentiating primary progressive aphasias in a brief sample of connected speech. *Neurology, 81*(4), 329-336. doi: 10.1212/WNL.0b013e31829c5d0e

Ash, S., Moore, P., Antani, S., McCawley, G., Work, M., & Grossman, M. (2006). Trying to tell a tale: discourse impairments in progressive aphasia and frontotemporal dementia. *Neurology, 66*(9), 1405-1413. doi: 10.1212/01.wnl.0000210435.72614.38

Baddeley, A. (2003). Working memory and language: an overview. *J Commun Disord, 36*(3), 189-208.

Baker, J., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke participants with aphasia. *Stroke, 41*(6), 1229-1236. doi: 10.1161/STROKEAHA.109.576785

Baldo, J., Schwartz, S., Wilkins, D., & Dronkers, N. (2010). Double dissociation of letter and category fluency following left frontal and temporal lobe lesions. *Aphasiology, 24*(12), 1593-1604. doi: 10.1080/02687038.2010.489260

Baldo, J., Schwartz, S., Wilkins, D., & Dronkers, N. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal Of The International Neuropsychological Society: JINS, 12*(6), 896-900.

Berko Gleason, J. (2005). *The development of language* (6th ed.). Boston, MA: Pearson Education, Inc.

Best, W., Greenwood, A., Grassly, J., Herbert, R., Hickin, J., & Howard, D. (2013). Aphasia rehabilitation: Does generalisation from anomia therapy occur and is it predictable? A case series study. *Cortex*, 49, 2345–2357.

Boersma, P. & Weenink, D. (2018). Praat: doing phonetics by computer [Computer program]. Version 6.0.37, retrieved 5 February 2018 from http://www.praat.org/.

Brownell, H. (1988). The neuropsychology of narrative comprehension. *Aphasiology,* 2:247–250.

Cattaneo, Z. (2011). Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. *Neuroscience, 183*, 64.

Chapados, C., & Petrides, M. (2013). Impairment only on the fluency subtest of the Frontal Assessment Battery after prefrontal lesions. *Brain, 136*(Pt 10), 2966-2978.

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 Topogr, 29*(5), 738-751. doi: 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. *J Alzheimers Dis, 39*(4), 799-808. doi: 10.3233/JAD-131427

Croot, K., Nickels, L., Laurence, F., & Manning, M. (2009). Impairment- and activity/participation-directed interventions in progressive language impairment: Clinical and theoretical issues. *Aphasiology, 23*(2), 125-160.

Croot, K., Taylor, C., Abel, S., Jones, K., Krein, L., Hameister, I., Ruggero, L., & Nickels, L. (2015). Measuring gains in connected speech following treatment for word retrieval: a study with two participants with primary progressive aphasia. *Aphasiology,* 29:11, 1265-1288.

Covington, M. (2007). CASPR research report 2007–05. Atheus, GA: 2007. *MATTR user manual.*

Demir, Ö., Levine, S., & Goldin-Meadow, S. (2015). A tale of two hands: Children's gesture use in narrative production predicts later narrative structure in speech. *Journal of Child Language, 42*(3):662-81.

Demir, Ö., Rowe, M., Heller, G., Goldin-Meadow, S., & Levine, S. (2015). Vocabulary, syntax, and narrative development in typically developing children and children with early unilateral brain injury: Early parental talk about the there-and-then matters. *Developmental Psychology, 51*(2), 161–175.

Falconer, C. & Antonucci, S. (2011). Use of semantic feature analysis in group discourse treatment for aphasia: Extension and expansion. *Aphasiology,* 26:1, 64-82.

Fergadiotis, G., Wright, H., & West, T. (2013). Measuring Lexical Diversity in Narrative Discourse of People With Aphasia. *American Journal of Speech-Language Pathology, American Speech-Language-Hearing Association*, 22(2), 10.1044/1058–0360(2013/12–0083). http://doi.org/10.1044/1058-0360(2013/12-0083)

Fiori, V. (2011). Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic participants. *Journal of Cognitive Neuroscience, 23*(9), 2309.

Flöel, A., Rösser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *J Cogn Neurosci, 20*(8), 1415-1422. doi: 10.1162/jocn.2008.20098

Forman, M., Farmer, J., Johnson, J., Clark, C., Arnold, S., Coslett, H., . . . Grossman, M. (2006). Frontotemporal dementia: clinicopathological correlations. *Ann Neurol, 59*(6), 952-962. doi: 10.1002/ana.20873

Fraser, K., Meltzer, J., Graham, N., Leonard, C., Hirst, G., Black, S., & Rochon, E. (2014). Automated classification of primary progressive aphasia subtypes from narrative speech transcripts. *Cortex, 55*(1), 43-60.

Fridriksson, J. (2011). Measuring and inducing brain plasticity in chronic aphasia. *J Commun Disord, 44*(5), 557-563. doi: 10.1016/j.jcomdis.2011.04.009

Fridriksson, J., Hubbard, H., & Hudspeth, S. (2012). Transcranial brain stimulation to treat aphasia: a clinical perspective. *Semin Speech Lang, 33*(3), 188-202. doi: 10.1055/s-0032-1320039

Fridriksson, J., Richardson, J., Baker, J., & Rorden, C. (2011). Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. *Stroke, 42*(3), 819-821. doi: 10.1161/STROKEAHA.110.600288

Gervits, F., Ash, S., Coslett, H., Rascovsky, K., Grossman, M., & Hamilton, R. (2016). Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study. *Brain Lang, 162,* 35-41. doi: 10.1016/j.bandl.2016.05.007

Gill, J., Shah-Basak, P., & Hamilton, R. (2015). It's the thought that counts: Examining the task-dependent effects of transcranial direct current stimulation on executive function. *Brain Stimulation, 8*(2), 253-259.

Gola, K., Thorne, A., Veldhuisen, L., Felix, C., Hankinson, S., Pham, J., … Rankin, K. (2015). Neural Substrates of Spontaneous Narrative Production in Focal Neurodegenerative Disease. *Neuropsychologia*, *79*(Pt A), 158–171. http://doi.org/10.1016/j.neuropsychologia.2015.10.022

Goodglass, H. & Kaplan, E. (1983). *Boston Diagnostic Aphasia Examination.* Media, PA: Williams & Wilkins.

Gorno-Tempini, M., Hillis, A., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S., . . . Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76*(11), 1006-1014. doi: 10.1212/WNL.0b013e31821103e6

Grossman, M. (2010). Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol, 6*(2), 88-97. doi: 10.1038/nrneurol.2009.216

Helm-Estabrooks, N. (2002). Cognition and aphasia: a discussion and a study. *Journal of Communication Disorders, 35*(2), 171-186. doi: 10.1016/S0021-9924(02)00063-1

Hilari, K., Byng, S., Lamping, D., & Smith, S. (2003). Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39): evaluation of acceptability, reliability, and validity. *Stroke, 34*(8), 1944-1950.

Horvath, J., Forte, J., & Carter, O. (2015). Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimul, 8*(3), 535-550. doi: 10.1016/j.brs.2015.01.400

Hung, J., Bauer, A., Grossman, M., Hamilton, R., Coslett, H., & Reilly, J. (2017). Semantic Feature Training in Combination with Transcranial Direct Current Stimulation (tDCS) for Progressive Anomia. *Front Hum Neurosci, 11*, 253. doi: 10.3389/fnhum.2017.00253

IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Indefrey, P. (2011). The spatial and temporal signatures of word production components: a critical update. *Front. Psychol.* 2:255. doi: 10.3389/fpsyg.2011.00255

Indefrey, P., and Levelt, W. (2004). The spatial and temporal signatures of word production components. *Cognition* 92, 101–144.

Kang, H., Baik, Y., Go, S., Kim, J., Park, K., Choi, K., & Jeong, J. (2010). Anatomical correlates of primary progressive aphasia subtypes using SPGR 3D volumetric analysis. *Alzheimer's & Dementia, 6*(4), S423.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test.* Philadelphia, PA: Lea & Febiger.

Kertesz, A., McMonagle, P., Blair, M., Davidson, W., & Munoz, D. (2005). The evolution and pathology of frontotemporal dementia. *Brain, 128*(Pt 9), 1996-2005. doi: 10.1093/brain/awh598

Kertesz, A., Raven, J., & PsychCorp (Firm). (2007). *WAB-R: Western Aphasia Battery-Revised.* San Antonio, TX: PsychCorp.

Kleim, J. & Jones, T. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research: JSLHR.* 2008;51:S225–239.

Knopman, D., Kramer, J., Boeve, B., Caselli, R., Graff-Radford, N., Mendez, M., Miller, B., Mercaldoet, N. (2008). Development of methodology for conducting clinical trials in fronto-temporal lobar degeneration. *Brain*, *131*(Pt 11):2957–2968.

Lefaucheur, J. (2016). A comprehensive database of published tDCS clinical trials (2005-2016). *Neurophysiol Clin, 46*(6), 319-398. doi: 10.1016/j.neucli.2016.10.002

Libon, D., Xie, S., Wang, X., Massimo, L., Moore, P., Vesely, L., . . . Grossman, M. (2009). Neuropsychological decline in frontotemporal lobar degeneration: a longitudinal analysis. *Neuropsychology, 23*(3), 337-346. doi: 10.1037/a0014995

Lincoln, N. (1982). The speech questionnaire: an assessment of functional language ability. *Int Rehabil Med, 4*(3), 114-117.

Looi, C., Duta, M., Brem, A., Huber, S., Nuerk, H., & Cohen Kadosh, R. (2016). Combining brain stimulation and video game to promote long-term transfer of learning and cognitive enhancement. *Sci Rep, 6*, 22003. doi: 10.1038/srep22003

MacWhinney, B. (2000). The CHILDES Project: Tools for Analyzing Talk. 3rd Edition. Mahwah, NJ: Lawrence Erlbaum Associates.

Mack, J., Chandler, S., Meltzer-Asscher, A., Rogalski, E., Weintraub, S., Mesulam, M., & Thompson, C. (2015). What do pauses in narrative production reveal about the nature of word retrieval deficits in PPA? *Neuropsychologia, 77*, 211-222.

Marangolo, P., Fiori, V., Campana, S., Calpagnano, M., Razzano, C., Caltagirone, C., & Marini, A. (2014). Something to talk about: enhancement of linguistic cohesion through tdCS in chronic non fluent aphasia. *Neuropsychologia*, *53*, 246-256.

McConathey, E., White, N., Gervits, F., Ash, S., Coslett, H., Grossman, M., & Hamilton, R. (2017). Baseline Performance Predicts tDCS-Mediated Improvements in Language Symptoms in Primary Progressive Aphasia. *Front Hum Neurosci, 11*, 347. doi: 10.3389/fnhum.2017.00347

Meinzer, M., Jähnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., . . . Flöel, A. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50*, 137-147. doi: 10.1016/j.cortex.2013.07.013

Meinzer, M., Lindenberg, R., Sieg, M., Nachtigall, L., Ulm, L., & Flöel, A. (2014). Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults. *Front Aging Neurosci, 6*, 253. doi: 10.3389/fnagi.2014.00253

Mesulam, M. (2001). Primary progressive aphasia. *Annals of neurology, 49*(4), 425-432.

Mesulam, M. (2007). Primary progressive aphasia: a 25-year retrospective. *Alzheimer Dis Assoc Disord, 21*(4), S8-S11. doi: 10.1097/WAD.0b013e31815bf7e1

Mesulam, M., Wieneke, C., Thompson, C., Rogalski, E., & Weintraub, S. (2012). Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain, 135*(Pt 5), 1537-1553. doi: 10.1093/brain/aws080

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M., . . . Walsh, V. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimul, 1*(4), 326-336. doi: 10.1016/j.brs.2008.07.002

Monte-Silva, K., Kuo, M., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul, 6*(3), 424-432. doi: 10.1016/j.brs.2012.04.011

Monti, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. *J Neurol Neurosurg Psychiatry, 79*, 451-453.

Nitsche, M., Liebetanz, D., Antal, A., Lang, N., Tergau, F., & Paulus, W. (2003). *Modulation of cortical excitability by weak direct current stimulation-technical, safety and functional aspects* (Vol. 56).

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

Norise, C., Sacchetti, D., & Hamilton, R. (2017). Transcranial Direct Current Stimulation in Post-stroke Chronic Aphasia: The Impact of Baseline Severity and Task Specificity in a Pilot Sample. *Front Hum Neurosci, 11*, 260. doi: 10.3389/fnhum.2017.00260

Peach, R., & Reuter, K. (2009). A discourse-based approach to semantic feature analysis for the treatment of aphasic word retrieval failures, *Aphasiology*, 24:9, 971-990. DOI: 10.1080/02687030903058629

Rider, J., Wright, H., Marshall, R., & Page, J. (2008). Using semantic feature analysis to improve contextual discourse in adults with aphasia. *American journal of speech-language pathology, 17*(2), 161-172.

Rizzo, V., Terranova, C., Crupi, D., Sant'angelo, A., Girlanda, P., & Quartarone, A. (2014). Increased Transcranial Direct Current Stimulation After Effects During Concurrent Peripheral Electrical Nerve Stimulation. *Brain Stimulation, 7*(1), 113-121.

Sparing, R., Dafotakis, M., Meister, I. G., Thirugnanasambandam, N., & Fink, G. (2008). Enhancing language performance with non-invasive brain stimulation--a transcranial direct current stimulation study in healthy humans. *Neuropsychologia, 46*(1), 261-268. doi: 10.1016/j.neuropsychologia.2007.07.009

Stagg, C., & Nitsche, M. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist, 17*(1), 37-53. doi: 10.1177/1073858410386614

Teichmann, M., Lesoil, C., Godard, J., Vernet, M., Bertrand, A., Levy, R., . . . Valero-Cabré, A. (2016). Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. *Ann Neurol, 80*(5), 693-707. doi: 10.1002/ana.24766

Terney, D., Antal, A., & Paulus, W. (2008). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *Brain Stimulation, 1*(3), 255-256.

Thompson, C., Cho, S., Hsu, C.-J., Wieneke, C., Rademaker, A., Weitner, B., . .. Weintraub, S. (2012). Dissociations between fluency and agrammatism in primary progressive aphasia. *Aphasiology, 26*(1), 20-43.

Tippett, D., Hillis, A., & Tsapkini, K. (2015). Treatment of Primary Progressive Aphasia. *Curr Treat Options Neurol, 17*(8), 362. doi: 10.1007/s11940-015-0362-5

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

Turkeltaub, P., Benson, J., Hamilton, R., Datta, A., Bikson, M., & Coslett, H. (2012). Left lateralizing transcranial direct current stimulation improves reading efficiency. *Brain stimulation, 5*(3), 201-207.

Vallar, G. (2006). Memory systems: The case of phonological short-term memory. A festschrift for Cognitive Neuropsychology. *Cogn Neuropsychol, 23*(1), 135-155. doi: 10.1080/02643290542000012

Vander Woude, A. (2017). *Connected language in primary progressive aphasia: testing the utility of linguistic measures in differentially diagnosing PPA and its variants.* Unpublished master's thesis, University of Maryland, College Park, Maryland.

Wang, J., Wu, D., Chen, Y., Yuan, Y., & Zhang, M. (2013). Effects of transcranial direct current stimulation on language improvement and cortical activation in nonfluent variant primary progressive aphasia. *Neurosci Lett, 549*, 29-33. doi: 10.1016/j.neulet.2013.06.019

Wilson, S., Henry, M., Besbris, M., Ogar, J., Dronkers, N., Jarrold, W., . . . Gorno-Tempini, M. (2010). Connected speech production in three variants of primary progressive aphasia. *Brain, 133*(Pt 7), 2069-2088. doi: 10.1093/brain/awq129

Wilson, S., Ogar, J., Laluz, V., Growdon, M., Jang, J., Glenn, S., . . . Gorno-Tempini, M. (2009). Automated MRI-based classification of primary progressive aphasia variants. *NeuroImage, 47*(4), 1558-1567.

Wisenburn, B., & Mahoney, K. (2009). A meta-analysis of word-finding treatments for aphasia. *Aphasiology, 23*(11), 1338-1352. doi: 10.1080/02687030902732745

Wright, H. & Capilouto, G. (2009). Manipulating task instructions to change narrative discourse performance. *Aphasiology, 23*:10, 1295-1308.

Wright, H., Capilouto, G., Srinivasan, C., & Fergadiotis, G. (2011). Story Processing Ability in Cognitively Healthy Younger and Older Adults. *Journal of Speech, Language, and Hearing Research : JSLHR, 54*(3), 900–917.