Perelman School of Medicine
University of Pennsylvania

Using Transcranial Direct Current Stimulation to Reveal Mechanisms of Language Loss and to Treat Progressive Aphasia Associated with FTD and Related Dementias

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List of Abbreviations

AD – Alzheimer's Disease

CCRS – Communication Confidence Rating Scale for Aphasia

CILT – Constraint-Induced Language Therapy

DDK - Diadochokinetic

DOD- Department of Defense

FTD – Frontotemporal dementia

FTLD - Frontotemporal lobar degeneration

lvPPA - logopenic variant Primary Progressive Aphasia

LTROG - Linguistic test for reception of grammar

PMC – Penn Memory Center

PPA: Primary Progressive Aphasia

PPT- Pyramids and Palm Trees

PRT - Philadelphia Repetition Test

mCILT – Modified constraint induced language therapy

NACC - National Alzheimer's Center Cohort

naPPA – non-fluent / agrammatic Primary Progressive Aphasia

NWRT – Non-word Repetition Test

svPPA – Semantic variant Primary Progressive Aphasia

tDCS – Transcranial Direct Current Stimulation

WAB: Western Aphasia Battery

WAB-AQ: Western Aphasia Battery – Aphasia Quotient

VAMC: Veteran Affairs Medical Center

Study Summary

Title	*Using Transcranial Direct Current Stimulation to Reveal Mechanisms of Language Loss and to Treat Progressive Aphasia Associated with FTD and Related Dementias*
Short Title	*PPA DOD*
IRB Number	*843286*
Phase	*Phase 2*
Methodology	*Double-blind, sham controlled, crossover design*
Study Duration	*12 months*
Study Center(s)	*Single-center*
Objectives	*Primary – Characterize tDCS treatment mechanisms by identifying responders to stimulation* *Secondary – Reveal structural and functional brain connections that predict response to tDCS.*
Number of Subjects	*62*

Main Inclusion and Exclusion Criteria	*Between the ages of 45-80* *Diagnosis of PPA* *Native English Speaker* *No additional neurological disease*
Investigational Product (drug, biologic, device, etc.)	
For Device include the planned use	*We will be using a commercially available tDCS device manufactured by NeuroConn.*
For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment	Two 5x5 electrodes at 1.5 mA; anode=F7, cathode = O1.
Duration of administration (if applicable)	Stimulation will take place over 2 weeks; 10 sessions for 20 minutes each.
Reference therapy	*Sham tDCS*
Statistical Methodology	Linear Mixed Models will be used to compare the performance of subjects receiving real tDCS to subjects receiving sham tDCS on change in WAB-AQ scores.
Safety Evaluations	*Subject reports of adverse events will serve as the primary measure of safety.*
Data and Safety Monitoring Plan	*PI will oversee safety and data monitoring*

BACKGROUND AND STUDY RATIONALE

This document is a protocol for a clinical research study. This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including US and international standards of Good Clinical Practice.

1. Introduction

Primary Progressive Aphasia (PPA), a condition affecting 20-40% of patients with frontotemporal lobar degeneration (FTLD) disorders and a smaller proportion of patients with Alzheimer's disease (AD), is characterized by progressive deterioration of language function (Mesulam, 2001). There are currently three recognized variants of PPA: non-fluent/agrammatic, logopenic, and semantic. Non-fluent/agrammatic (naPPA) and logopenic (lvPPA) variant are both characterized by difficulties with speech-language production; naPPA typically involves grammatical simplification, effortful speech, and speech apraxia, while lvPPA is associated with phonological errors and poor word retrieval/repetition. Semantic variant PPA (svPPA) involves anomia, reduced expressive vocabulary, and single-word comprehension deficits (Gorno-Tempini et al., 2011). All forms of PPA profoundly impact communication ability and impose a significant burden on patients and their caregivers (Riedijk et al., 2006; Mioshi, et al., 2009; Diehl-Schmid et al., 2013; Mioshi et al., 2013). Speech and language therapies for PPA have shown positive but only modest results (Henry et al., 2008; Croot et al., 2009, 2015; Beeson, 2011; Jokel et al., 2014), and medications used to treat dementias are ineffective. Thus, development of new treatments that can reverse, arrest, or significantly slow language loss in persons with PPA would represent a tremendous step forward for those suffering from this debilitating condition.

1.1 Background and Relevant Research

1.1.1 Neurodegeneration in PPA variants

Specific language deficits that emerge in persons with different PPA variants relate to the regions of the left hemisphere language networks that are selectively affected by neurodegeneration (Grossman, 2010). Atrophy is observed in the left inferior frontal lobe and insula in persons with naPPA. Individuals with lvPPA show atrophy of the left posterior temporal and parietal lobes. Semantic variant PPA (svPPA) involves atrophy of the anterior and ventral temporal lobe (Grossman, 2012; 2018; Agosta et al., 2013; Giannini et al., 2017). Thus, each PPA syndrome affects a portion of the neural network supporting language, while other portions of the language network remain relatively preserved. Unfortunately, while our expanding understanding of the anatomic, neural, and functional properties of language networks has enabled greater insight into the neural changes that underlie PPA symptoms, there are no approved therapies that leverage this knowledge in order to advance targeted treatments for neurodegenerative aphasias.

1.1.2 tDCS to treat PPA

Transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique, is a promising intervention in aphasia. TDCS delivers low-intensity electrical current to the brain through electrodes placed on the scalp. This low-intensity current can producing small shifts in the resting membrane potential of large numbers of neurons which is believed to alter neuronal firing rates and thus modulates patterns of brain activity (Bindman et al.,1964; Stagg & Nitsche, 2011; Rahman et al., 2013). Evidence indicates that repeated stimulation with tDCS can result in lasting changes in cognitive performance (e.g. Ries et al., 2009; Flöel et al., 2012). A number

of studies indicate that tDCS may serve as an effective intervention for aphasia (Reviewed in Norise & Hamilton, 2017). In our own prior work, we found that 10 days of tDCS in subjects with post-stroke aphasia resulted in a ~17% improvement in aphasia severity, compared to sham tDCS. This improvement was measured two months after discontinuation of stimulation (Shah-Basak et al., 2016).

To date, only a handful of studies have investigated the utility of tDCS in persons with PPA. An early case study of one individual with naPPA demonstrated improvements in auditory word-picture identification, picture naming, oral world reading, and word repetition in the absence of speech therapy after five days of tDCS applied over the left posterior region and the left inferior frontal gyrus (LIFG) (Wang et al., 2013). Cotelli and colleagues (2014) found that 10 sessions of tDCS over the left dorsolateral prefrontal cortex combined with individualized speech therapy led to improved picture-naming in a small sample of subjects with naPPA who received tDCS compared to sham stimulation; the benefit lasted up to 12 weeks post-stimulation. More recently, a double-blind, sham-controlled cross-over design study involving 12 subjects with svPPA found that bilateral tDCS to the temporal poles transiently improved semantic accuracy in persons with svPPA (Teichmann et al., 2016).

Our lab conducted a pilot study in a small cohort of subjects with PPA (n=6; 4 lvPPA; 2 naPPA) to determine the feasibility of delivering ten sessions of tDCS to the left hemisphere with follow-up testing immediately after, six weeks, and twelve weeks after stimulation. In order to engage the language network during tDCS, subjects performed an unstructured language task during stimulation in which they verbally narrated wordless children's books. We saw significant improvement in measures of speech production, grammatical comprehension, and semantic processing, which persisted up to twelve weeks post-stimulation (Gervits et al., 2016. We next conducted a randomized, sham-controlled crossover pilot study of the same stimulation approach with follow-up testing two and twelve weeks after stimulation. In a cohort of 7 subjects (1 lvPPA; 6 naPPA), we found beneficial effects of stimulation on global language performance (McConathey et al., 2017). Attrition in these studies was low (~15%).

1.1.3 Combining CILT with tDCS

The idea of pairing speech therapy with tDCS is compelling because tDCS is believed to work by modulating existing neural activation patterns, strengthening or weakening their representations via neuroplasticity (Reato et al., 2013; Jackson et al., 2016). By this account, cognitive activities paired with stimulation determine which patterns of neural activity are reinforced by tDCS, and thus which mental abilities are selectively modulated. Domain-specific training tasks have been paired with tDCS to achieve substantive, long-lasting effects (Reis et al., 2009; Friel et al., 2017; Ruf et al., 2017), and stimulation has been successfully paired with therapies in neurorehabilitation studies (Page et al., 2015; de Aguiar et al., 2015; Mortensen et al., 2016; Viana et al., 2014). We believe that tDCS in persons with PPA will be most effective when paired with a behavioral intervention that engages the language system. We have recently shown that pairing tDCS with a 2-week regimen of a semantic feature training therapy (Boyle, 2004; Hashimoto & Frome, 2011) can improve naming impairments in subjects with severe anomia (svPPA or lvPPA, n = 4; AD, n=1; Hung et al., 2017). Other studies in both post-stroke aphasia and PPA demonstrate that pairing behavioral language intervention with stimulation can result in benefits that generalize beyond trained language items, including improvement in more global measures of aphasia severity (Shah-Basak et al., 2015; Gervits et al., 2016). The current project will employ a modified version of constraint induced language therapy (mCILT), which requires subjects to engage with stimuli verbally with increasing degrees of articulatory complexity (Pulvermüller et al., 2001; Maher et al., 2006). Owing to the task demands of the therapy, mCILT is well-suited to patients with speech production deficits (Pulvermuller et al., 2001; Maher et al., 2006; Breier et. Al., 2009) and has been used successfully in patients with

naPPA (Hameister et al., 2017). This study also builds upon our prior success using a similar therapy in persons with nonfluent post-stroke aphasia (Shah-Basak et al., 2015; Norise et al., 2017).

1.1.4 Using brain networks to predict tDCS response

Evidence points toward the importance of brain network hubs—nodes that are connected to many other nodes by edges—in neurodegenerative disorders. Nodes with high hub centrality are critical participants in a wide range of network operations supporting cognitive functions (van den Heuvel & Sporns, 2013) and are disproportionally affected in neurological syndromes (Stam, 2014). The tendency for a node to be a hub can be distinguished from more general measures such as network density, the total number of connections in a network, and can be expressed as a hub score, which quantifies the centrality of a node in information processing in a network (van den Heuvel, 2010). Brain regions with especially high hub scores participate in many processing pathways within the brain. Across the spectrum of neurodegenerative disorders, it is suspected that as nodes in critical brain areas are progressively degraded by disease, this is associated with changes in the recruitment of remaining hub nodes (Stam, 2014). Early in the course of degenerative disease, as specific brain regions are selectively affected, it is believed that there is an *increase* in the connectivity of remaining hubs in those regions that partially compensates for lost nodes and helps to maintain performance (Stam, 2014). However, as worsening disease leads to greater node loss, these compensatory changes cannot keep pace with neurodegenerative deterioration, resulting in decreasing hub scores in affected regions (Buckner et al., 2009; Engels et al., 2015). Eventually, when degenerated regions are severely affected, hub scores decline dramatically as the few remaining nodes do not harbor sufficient connections to contribute to networks. In the case of PPA, residual language abilities would then depend on the activity of relatively spared language regions. In a preliminary analysis of 65 subjects with PPA we found that hub scores are indeed decreased in different language centers in PPA variants. Thus, the hub score could serve as a metric in PPA to describe how affected and spared regions impact network functions at different stages of disease. Brain network hubs could also be positively influenced by interventions that enhance their connectivity. We posit that changes in hub scores could also provide a framework for understanding the impact of tDCS on language networks in persons with PPA.

1.2 Name and Description of the Investigational Product

We will be using a commercially available tDCS devices manufactured by neuroConn, the programmable direct current stimulator. This device is powered by rechargeable batteries and includes a microprocessor controlled unipolar and bipolar constant source for stimulation. This tDCS unit has built-in blinding capabilities, which allows the administrator to enter in a numerical code that corresponds with either sham or real stimulation parameters.

1.3 Dose Rationale (if applicable)

Participants will undergo 10 sessions (Monday-Friday, 2 weeks) of tDCS for 20 minutes using a montage where the anode (1.5 mA) is placed over F7 (left frontotemporal lobe) and the cathode will be place on O1 (left occipital) using the 10-20 EEG mapping system. These stimulation parameters adhere to those used in our prior work (Gervits et al., 2016; Price et al., 2016) and other studies of tDCS in PPA (Norise & Hamilton, 2017).

2 Study Objectives

2.1 Primary Objective

- To determine the efficacy of tDCS + mCILT in improving language performance in persons with PPA compared to sham tDCS + mCILT.

2.2 Secondary Objectives

- Utilized network analyses to directly interrogate the roles of structural and function connectively in the language network in PPA.
    - Determine whether baseline hub characteristics of the language systems of persons with naPPA/lvPPA,and svPPA influence aphasia severity.
    - Determine whether tDCS induced behavioral effects induce changes in the language network properties.
    - Determine whether structural and functional connectivity features can predict responsiveness to tDCS.

3 Investigational Plan

3.1 General Design

This is a double-blind, sham-controlled, crossover study. Groups will be counterbalanced according to PPA subtype. All participants will undergo baseline language testing and neuroimaging prior to receiving 10 treatment sessions over 2 weeks (Monday-Friday) of either real or sham tDCS paired with mCILT. Immediate post-treatment, 6 week and 12 week follow-ups will be obtained. Participants will then crossover into the second portion of the study whereby they will receive the opposite treatment protocol (real or sham tDCS + mCILT) and an additional 24 week follow-up. Treatment must take place within 2 days to 4 weeks of baseline testing. The overall timeline for each subject's participation is indicated below in Figure 1.

Figure 1: Timeline for each subject

Enrollment	Baseline MRI	Baseline 1	Baseline 2	Treatment	Follow-up	Follow-up MRI	6 week Follow-up	12 week Follow-up	12 week Follow-up MRI
SCREENING	VISIT 1**	VISIT 2*	VISIT 3*	Visit 4-13	VISIT 14*	VISIT 15**	VISIT 16*	VISIT 17*	VISIT 18**
- Informed Consent - Screening Forms - Demographics Form	**MRI**	**-CCRSA -WAB 1 -CILT 1 -NWRT -LTROG Oral -PPT Picture -NACC Word Reading -NACC Sentence Repetition**	**-WAB 2 -CILT 2 -PRT -DDK -LTROG Written -PPT Words -Story -NACC Sentence Reading**	**tDCS + mCILT OR Sham tDCS + mCILT**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**	**MRI**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**	**-CCRSA -WAB 1 -CILT 1 -NWRT -LTROG Oral -PPT Picture -NACC Word Reading -NACC Sentence Repetition**	**MRI**
~ 1 hour	~ 1 hour	~ 3 hrs	~ 3 hrs	~ 1.5 hrs	~ 3 hrs	~ 1 hour	~ 3 hrs	~ 3 hrs	~ 1 hour

Crossover Baseline	Crossover Treatment	Crossover Follow-up	Crossover Follow-up MRI	Crossover 6 week Follow-up	Crossover 12 week Follow-up	Crossover 12 week Follow-up MRI	Crossover 24 week Follow-up
VISIT 19*	VISIT 20-29	VISIT 30*	VISIT 31**	VISIT 32*	VISIT 33*	VISIT 34**	Visit 35
-WAB 2 -CILT 2 -PRT -DDK -LTROG Written -PPT Words -Story -NACC Sentence Reading	**tDCS + CILT OR Sham tDCS + CILT**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**	**MRI**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**	**MRI**	**- WAB - CILT - NWRT - PRT - LTROG Oral & Written - PPT Picture & Words - NACC Word reading, Sentence Reading & Repetition - DDK - CCRSA - Story**
~ 3 hours	~ 1.5 hours	~ 3 hours	~ 1 hour	~ 3 hours	~ 3 hours	~ 1 hour	~ 3 hours

* Depending on patient's schedule / fatigue levels, language assessment visits may be accomplished over two to three visits instead of one. To reduce burden of extra visits, language assessments may also be completed at day 1 treatment, prior to the start of the treatment itself.

**Depending on patient's schedule / fatigue levels, MRI visits may be combined with another visit.

3.1.1 Screening Phase

Subjects will be recruited from the large, well-characterized research cohort of the Penn FTD Center. Interested subjects will participate in a brief telephone screening to ensure that they meet basic study criteria including but not limited to age-range, geographic location and native language. Potential subjects eligible based off these criteria will be invited for a formal enrollment appointment where consent will be documented and more in-depth screening will take place. The enrollment appointment will be conducted in-person by the PI or a member of the research staff. Written consent will be obtained before formal screening documents are completed.

A remote screening visit may be conducted via Bluejeans. Before screening interview begins, remote consent will be obtained, with e-signatures collected via RedCAP.

3.1.2 Baseline Phase

The baseline phase will consist of 2-3 sessions, each lasting about 2-3 hours depending on the subject's stamina. The purpose of baseline testing is to characterize the subject's language

function. To that end, a number of standard language assessments will be administered. These include the Western Aphasia Battery (WAB), Pyramids and Palm Trees (PPT), Philadelphia Repetition Test (PRT), Non-word Repetition Test (NWRT), CILT stimulus naming, Linguistics Test for Reception Of Grammar (LTROG; written & oral), Diadochokinetic (DDK), Spontaneous story telling (Cinderella Story), National Alzheimer's Center Cohort (NAAC) tests, and Communication Confidence Rating Scale for Aphasia (CCRS). Depending on PPA severity, we may have to split these tests over two-three visits instead of one to accommodate for subject fatigue. Additionally, a baseline MRI scan of the brain will be conducted. No contrast will be used.

Baseline visits might be conducted via tele-assessment, using Bluejeans, or a HIPAA compliant alternative. In such cases, testing materials may be mailed to participants beforehand, and instructions provided during the tele-assessment. Other test materials will be displayed over the video software. Video and audio of the tele-assessment will be recorded.

3.1.3 Study Intervention Phase

In the treatment phase, there will be 10 sessions of tDCS + mCILT over 2 consecutive weeks (Monday-Friday) in which 20 minutes of 1.5mA tDCS will be delivered to the left hemisphere. During each treatment session, a 60-90 minute session of mCILT will be simultaneously performed.

3.1.4 Follow up Phase

There will be an immediate, 6-week and 12-week follow-up following both the initial component. The crossover component will have an additional 24 week follow-up. The full language assessment will be repeated at each follow-up. Subjects will also be asked to complete an MRI scan at the immediate and 12 week follow-ups. Depending on the patients stamina, language assessments may take three visits.

The follow-up visit may be conducted via tele-assessment.

3.1.5 Allocation to Interventional Group

Participants will be semi-randomized using a predetermined list generated by excel. Since this is a crossover study, all participants will eventually receive real stimulation - only the order will differ. Half of our participants will receive real tDCS first, and the other half will receive sham tDCS first. All participants will participate in mCILT.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint will be overall change in WAB-AQ between the first baseline visit and the 12 week follow-up (real tDCS compared to sham tDCS).

3.2.2 Secondary Study Endpoints

Change in accuracy on additional language assessment given over baseline & follow-up visits will serve as secondary outcomes.

3.2.3 Primary Safety Endpoints [if applicable]

The risks from language tasks and MRI imaging are minor. Data on adverse events occurring during the 4 weeks in which tDCS is being administered will be collected by asking subjects at the beginning and end of every session if they have noted any adverse effects or new symptoms since their most recent. Reports of adverse effects from tDCS and other aspects of the study (brain imaging, language tasks and mCILT) will serve as the primary safety endpoint.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Study subjects must meet all of the following inclusion criteria:

- Presence of aphasia attributable to Primary Progressive Aphasia.
- Between the ages of 45 and 80.
- Must be a native English speaker

4.2 Exclusion Criteria

- Cognitive impairment of sufficient severity to preclude them from participating in testing / therapy (MMSE < 15).
- History of seizures or unexplained loss of consciousness in the past 6 months
- Subjects with metallic objects in the face or head other than dental apparatus such as braces, fillings, and implants.
- Subjects with Pacemakers or ICDs.
- Subjects with previous craniotomy or any breach in the skull; skull defect could be associated with shunting of current leading to unpredictable location and level of current affecting the brain.
- Subjects with a history of stroke
- Subjects with history of TIA (at the PI's discretion, a TIA which occurred at least 6 months ago is okay if no other events have been observed)
- Subjects with a history of small vessel disease
- Use of sedation medication that may cause arousing the subject during testing difficult (must be free of meds that impair cognition for at least 3 months)
- Pregnancy

4.3 Subject

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

4.4 Duration of Study Participation

The duration of the study as outlined above is approximately 12 months depending on how quickly the treatment sessions begin after baseline testing.

4.5 Total Number of Subjects and Sites

We intend to enroll up to 62 subjects: 31 naPPA/lvPPA; 31 svPPA

Subjects will be stimulated and tested in HUP or Perelman School of Medicine buildings. Depending on the availability of rooms, four testing sites may be employed: Neurology out-patient offices in the Perelman Center, Neurology out-patient offices on Ravdin 2, laboratory of Dr. Grossman (Gibson 3), or laboratory of Dr. Roy Hamilton (Goddard). The tDCS device is portable and no special equipment is required.

Additionally, if it is requested by the participant, we may conduct study sessions in the participant's home. In order to be eligible for home visits, patients must live within 40 miles, or approximately one hours, of the University of Pennsylvania. Ultimately, the discretion for eligibility of home visits will be up to the Principal Investigator, in order to best effectively and efficiently manage the lab's resources. If participants do qualify for home visits, they will be required to come to the lab for their first stimulation session. If the patient does not experience any adverse events during that stimulation session and if the other requirements are met, then all subsequent stimulation sessions would be conducted in the participant's home. Again, we would like to stress that this is only an option, not a requirement, which participants may choose if it is more convenient for them. Study visits not requiring the use of tDCS may be conducted at the participant's home if this situation proves to be more convenient for the participant.

4.6 Vulnerable Populations:

Children, fetuses, neonates, or prisoners are not included in this protocol.

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken

in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

We will be using a commercially available tDCS devices manufactured by NeuroConn. This device is powered by rechargeable batteries and built-in blinding capabilities.

tDCS will be paired with simultaneous mCILT.

5.2 Intervention Regimen

tDCS will use two 5x5 electrodes, housed in saline soaked sponges, placed directly on the scalp. One electrode (anode) is placed over the targeted region of cortex (F7) and an electrode of opposite polarity (cathode) is placed over the left occipital cortex (O1). Stimulation will be administered at 1.5 mA in intensity and for 20 minutes per session. Sham stimulation will include a 30-second ramp-up and ramp down periods.

5.2.1 Constraint Induced Language Therapy (CILT)

Participants will begin 10 sessions of mCILT+ tDCS (or mCILT+sham tDCS) between 2 – 30 days after baseline. Each mCILT session will last 1 to 1.5 hours, during the first 20 minutes of which mCILT will be paired with active or sham tDCS.

The progression of mCILT during therapy will go as follows: Treatment begins with single noun requests, with cuing as needed until the subject performs ≥ 80% accuracy over two trials of 64 (32 treated, and 32 untreated) items with minimum assistance, at which point the action words will be added and the response demand increases to object + action phrases; cuing will be increased and task demands decreased if accuracy falls below 50% until it returns to 75% with minimum assistance. Treatment will progress using these criteria: high then low frequency nouns, verbs, agent noun + verb, and then to sentences of increased length and complexity. Throughout the course of a CILT treatment, the difficulty of each stage of therapy will be scaled to individual participant performance, such that participants' language abilities can be behaviorally "shaped" in a sequential manner to ensure a low rate of failure and a gradual increase of difficulty as improvements are made and new skills are retained. The main communication goals of mCILT are to enhance accuracy, speed, and grammatical complexity of participants' speech.

Note that we will use a modified version of the CILT (mCILT). The modification of CILT includes semantically related noun-verb pairs, a modification that may be better suited to address syntactic structure. We will use a specially designed barrier with a whole cut out that will allow for the tDCS machine to be passed through and monitored by the administrator, but still block the view between participant & researcher. The administrator will be trained not to respond to the nonverbal communication. Participants may use writing as a strategy for self-cuing, if helpful. In these cases, the administrator will provide them with a piece of paper and writing utensil while reminding the participant that they are still required to provide a spoken response to achieve the objective of obtaining a matching card.

All sessions will be digitally video/audio recorded for offline scoring (this will ensure data quality and also allow for additional metrics such as assessing latency to respond)."

5.3 Storage

The tDCS unit will be stored in a locked room in Goddard Labs in which the lab's devices are stored. Only the PI and other members of his research team have keys to this room. When not in use, the unit will be enclosed in a special, dedicated storage container that will be marked

with a statement that the enclosed unit is not to be used for clinical purposes. Additionally, the unit itself will be clearly marked with a statement indicating that it is an investigational instrument only.

5.4 Blinding

tDCS units have a built in blinding feature via the use of assigned codes which will run specific device parameters.

A master excel file of subjects assignments will be kept by the un-blinded study coordinator. When a subject is randomized, the research team will receive a code to enter into the tDCS unit prior to stimulation. This code will run either a real or sham session. The blinding may be broken in the case of an emergency. To request un-blinding the PI will be informed of the reason for un-blinding and if in agreement will allow the coordinator to tell the researcher what the code means.

5.5 Administration and Accountability

All stimulation sessions will be logged on a daily stimulation summary sheet. These logs will be kept with the subject's data in a secure location in the lab space. This log will include the date of stimulation, the individual administering tDCS, blinding code used, and any notes regarding the session.

5.6 Subject Compliance Monitoring

Noncompliance with regard to the randomized intervention could occur if participants miss therapy sessions or if the wrong code is entered into the tDCS device. To minimize noncompliance due to missed therapy sessions, participants who miss up to 3 sessions will be allowed to make up missed sessions the following week. To avoid error in code entry, researchers will be asked to record the code used in each administration of tDCS in the daily log.

6 Study Procedures

6.1 Enrollment & Screening

The screening visit will consist of:

- Informed Consent + HIPAA
- Review of Inclusion/Exclusion Criteria
- Review of MRI Critiera
- Review of demographics / medical history
- Payment paperwork

The anticipated length of this visit is 30 minutes to 1 hour; depending on questions asked during the consent process and responses to screening questions.

Participants will be asked to stop any other speech or language therapies during the course of their study participation.

6.2 Study Intervention Phase

6.2.1 Visit 1 (Baseline MRI)

Subjects will undergo an MRI scan on a 3T Siemens unit; no contrast will be administered.

The anticipated time of this visit is 1 hour.

Depending on patient's schedule / fatigue levels, MRI visits may be combined with another baseline visit or screening.

6.2.2 Visit 2 (Baseline 1)

Subjects will undergo language testing to characterize their impairment:

- Western Aphasia Battery
- Pyramids and Palm Trees
- Philadelphia Repetition Test
- Non-Word Repetition Test
- CILT Baseline Assessment
- Linguistic test for reception of grammar
- Spontaneous Speech – Story telling
- Apraxia Measure – DDK
- National Alzheimer's Center Cohort Tests for FTD
- Communication Confidence Rating Scale for Aphasia

Testing is anticipated to take about 3 hours; however, if the testing length too long for the participant it is possible to split the visit in two. Participants must begin treatment phase of study within 4 weeks of completed baseline testing.

6.2.3 Visit 3 (Baseline 2)

Subjects will repeat full language battery from Visit 2 for reliability.

Testing is anticipated to take about 3 hours; however if the session is too long for the participant it is possible to split the visit in two.

6.3 Phase 2 of the Study (Visits 4-13)

In the treatment phase of the study there will be 10 daily (Monday-Friday) tDCS sessions over 2 consecutive weeks in which 20 minutes of 1.5mA stimulation will be delivered to the left frontotemporal lobe (F7). During stimulation, a 60-90 minute session of mCILT will be completed. The total anticipated time of these visits is about 60-90 minutes.

6.4 Follow Up Phase of the Study

6.4.1 Visit 14 (Immediate Follow-up)

All language assessments performed at baseline will be re-administered at follow-up to assess language function.

Testing is anticipated to take about 3 hours; however if the session is too long for the participant it is possible to split the visit in two.

6.4.2 Visit 15 (MRI Follow-up)

Subjects will undergo an MRI on a 3T Siemens unit; no contrast will be administered.

The anticipated time of this visit is 1 hour.

Depending on patient's schedule / fatigue levels, MRI visits may be combined with follow-up language testing.

6.4.3 Visit 16 (6 week Follow-up)

All language assessments performed at baseline will be re-administered at follow-up to assess language function.

Testing is anticipated to take about 3 hours; however if the session is too long for the participant it is possible to split the visit in two.

6.4.4 Visit 17 (12 week Follow-up)

All language assessments performed at baseline will be re-administered at follow-up to assess language function.

Testing is anticipated to take about 3 hours; however if the session is too long for the participant it is possible to split the visit in two.

6.4.5 Visit 18 (12 week Follow-up MRI)

Subjects will undergo an MRI scan on a 3T Siemens unit; no contrast will be administered.

The anticipated time of this visit is 1 hour.

Depending on patient's schedule / fatigue levels, MRI visits may be combined with follow-up language testing.

6.4.6 Visits 19-35 (Crossover)

Participants will crossover into the second half of the study after the 12 week follow-up. Visits 18 & 19 will serve as Baseline and then all study procedures will exactly match the first half of the study. The crossover will include an additional follow-up visit at 24 weeks.

6.5 Subject Withdrawal

Subjects are free to withdraw from the study at any time if they no longer wish to participate. Additionally, participants may be withdrawn from the study prior to the expected completion date for a number of reasons:

1) Any adverse outcome or event which may represent a possible health risk to the participant
2) Failure of the participant to adhere to protocol requirements
3) Worsening of language abilities, or worsening cognition or mood.
4) Change of PPA diagnosis

Abrupt discontinuation of tDCS is not associated with rebound effects or other adverse outcomes, so no alternative treatment or transitional therapy will be required if participants discontinue the protocol.

6.5.1 Data Collection and Follow-up for Withdrawn Subjects

Should participants wish to withdraw from the study entirely, attempts will be made to seek permission to obtain survival data on such patients throughout the protocol defined follow-up

period. It will be a high priority to try to obtain at least survival data on all patients lost to follow-up.

A number of attempts will be made to contact a participants by various means before he or she will be considered lost to follow-up. These methods will consist of three or more of phone calls to participant, followed by a phone call to their caregiver if possible, followed by a certified letter. Should all of these efforts fail to elicit a response the patient will be considered lost to follow-up.

6.6 Early Termination Visits

All subjects that decide to leave the study early or are asked to by the investigator will be strongly encouraged to continue follow-up visits, but early termination visits are not planned.

7 Study Evaluations and Measurements

7.1 Medical Record Review

- Date of birth
- Address
- Contact information (telephone / email)
- Hospital admission date and date of brain injury
- Past medical history as it relates to PPA and other neurologic conditions, cardiac status, and surgery
- Results of neuroimaging studies and dates, including MRI and/or CT exams
- Current and past medications or therapies

7.2 Physical Examination

Should subjects report new complaints or a change in their neurologic/language status, an examination will be performed by the PI or other neurologist working on the project.

7.3 Laboratory Evaluations

Participants will be asked to undergo high quality brain imaging via MRI at the University of Pennsylvania. We will obtain 3D T1-weighted MPRAGE images at a 1mm isotropic spatial resolution in order to provide anatomical data. Multiband resting-state fMRI data will be collected for ~10 minutes, at a resolution of 3x3x3 mm3(TR = 0.5s, TE = 30ms, 230x230 mm2 FoV, 128x128 acquisition matrix). Diffusion Spectrum Imaging (DSI) scans will sample 257 directions using a Q5 half shell acquisition scheme with a maximum b value of 5000 and an isotropic voxel size of 2.4mm. (Parameters: TR = 11.4s, TE = 138ms, 51 slices, FoV (231,231,123 mm,6 B0 images).

7.4 Pregnancy Testing

There is no known risk to a mother or fetus from tDCS or MRI, but due to the fact that the safety of the technique in pregnant women has not been fully studied, pregnant women are excluded from the study. If the female subject is of child-bearing age, a urine pregnancy test will be performed before the first tDCS sessions.

7.5 Other Evaluations, Measures

The following battery of language tasks will be administered prior to treatment and at 6 weeks and 12 weeks (& 24 weeks in crossover) after the completion of tDCS: (1) The Western Aphasia Battery (WAB; Shewan & Kertesz, 1980) samples a number of different language functions and

generates a summary score between 0-100 (Aphasia Quotient, AQ), interpretable as general aphasia severity. The WAB will be administered on two occasions prior to treatment to obtain a stable baseline. Word and non-word repetition tests from the Moss Psycholinguistic Aphasia Database (MAPPD; Dell et al, 1997; Sobel, Brecher, & Schwartz, 2006) will be used to further assess lexical and post-lexical phonological encoding. Word repetition will also be used to quantify instances of consonant distortion, prosodic alteration, and other features of speech apraxia. The Pyramids and Palm Trees test (Picture version; Howard & Patterson, 1992) will be used to assess core semantic memory. (5) The Communication Confidence Rating Scale for Aphasia (Babbitt, Cherney, & Halper, 2008) will be administered to assess changes in quality of communication in daily life. Spontaneous Speech as an indicator of functional communication will be assessed with the Cinderella story (Stark, 2010). The Linguistics Test for Reception of Grammar (LTROG, Bishop, 1989) will be administered to assess grammatically comprehension of speech and written language. Finally, 2 pre-treatment baselines will be obtained on the stimuli used for CILT. We note that the baseline sessions may require more than one day to complete.

7.6 Efficacy Evaluations

No interim analyses for efficacy are planned, as previous work suggests that the maximal benefit is likely to be obtained at the 12 week endpoint and there is no additional risk to the subject after the tDCS is completed.

7.7 Safety Evaluations

Although we consider the risk to be extremely low, subject safety will assessed throughout the course of the study by asking subjects if they have experienced adverse effects from the interventions. As any adverse effects of tDCS are likely to occur at the time of stimulation, we will ask all subjects before and immediately after tDCS if they note any symptoms of concern. This will be documented for each subject at each stimulation session.

8 Statistical Plan

8.1 Primary Endpoint

The primary endpoint will be overall change in WAB-AQ between the baseline visit and the 12 week follow-up visit (real compared to sham tDCS).

8.2 Secondary Endpoints

Change in accuracy on additional language assessment given over baseline & follow-up visits will serve as secondary outcomes. As well as any changes in fMRI data.

8.3 Sample Size and Power Determination

To calculate power, we started from an ambitious but realistic estimate of the population available at the participating recruitment sites. We intend to recruit 62 subjects, although 25 subjects will be adequate to detect a difference between real and sham stimulation within each group (alpha = 0.05; power = 0.8). Although our historical attrition rate has been 15%, we will conservatively anticipate of a 25% attrition rate and will therefore enroll 31 subjects in each PPA variant arm.

8.4 Statistical Methods

8.4.1 Treatment Effect on Language Performance

A linear mixed-effects model will be used to determine whether the change in performance induced by tDCS + mCILT for subjects in each PPA variant group differs significantly from that induced by sham stimulation, covarying for age, sex, education and disease duration at time of study if they are imbalanced between the two groups at baseline. The mixed model will include a fixed effect for sequence, period, treatment, and the interaction between treatment and period. A random intercept term will be included in the mixed-effects model to account for correlations from repeated outcome measures. Additional analyses will examine change in other language battery tests, and exploratory analysis will examine baseline aphasia severity as a predictor of response.

8.4.2 Identifying Predictors of Treatment response

We will employ a binary outcome (responder vs. non-responder), based on a change in WAB-AQ of 5 points, which has been recognized as clinically meaningful change in aphasia severity (Elman etal., 1999). We will pursue a series of univariate logistic regression analyses interrogating the following variables, in order to determine which are likely predictors of response to tDCS: PPA variant (naPPA/lvPPA, svPPA, extent of brain atrophy (cortical thickness in the designated language network regions), hub scores, and baseline symptom severity (baseline WAB-AQ). Akaike information criterion (AIC) will be used to develop and select a final model that includes the predictors of tDCS response previously identified as relevant in the univariate analyses. First, the full model containing all relevant predictors will be compared against models with one of each of the predictors removed, to evaluate the extent to which predictors may be correlated or may uniquely contribute to the model despite some potentially shared contribution. The final model will contain age, duration of disease, and sex as covariates and only those predictors identified as unique contributors to tDCS response by the AIC selection procedure.

8.4.3 Network Neuroscience measures of response to tDCS + CILT

We will first test for the hypothesized relationship between node loss and hub scores by expressing node loss as a quadratic term in a multiple regression using the gray matter thinning at each node in the language network to predict hub scores, covarying for subject age and disease onset, with an FDR-corrected threshold of 0.05. Then, we will use a data-driven machine learning approach—support vector regression—using multivariate hub scores (Fornito et al., 2015) throughout the brain to predict behavior. We will use a leave-one-out cross validation strategy to identify the combination of nonlinearly weighted variables that predict behavior. The value of the machine learning model will be evaluated in terms of percentage of variance explained relative to selecting a similarly sized set of random variables (neuroimaging features including region cortical thickness and individual white matter connections) in 10,000 permutations for both the traditional regression and support vector regression models. It will additionally be tested against network density—the total connectivity of the network—as a control condition. Then, to test whether strong hubs account for the greatest variance in the data, we will correlate the support vector regression weights with region hub scores post-hoc. A significant positive correlation would indicate that stronger hubs account for higher variance in behavioral scores.

We will then use multiple regression to assess stimulation condition as a predictive variable for each language network node. If the predictor illustrates that hub scores increase in the presence of active tDCS, we will test whether effects tend to be concentrated near the site of

stimulation using a permutation test in which we shuffle the assignment of significant nodes for each network statistic uniformly at random across the brain. If the number of nodes concentrated in the anterior perisylvian nodes encompassed by our area of stimulation is greater than 95% of permutations, it will establish that the effects of mCILT or tDCS + mCILT are local to this region. Moreover, it will allow us to examine whether the effects of stimulation on hub scores are observed in different PPA phenotypes that express pathology at the site of stimulation (as in our naPPA/lvPPA subject) or remote from the site of stimulation (as in our svPPA subjects). Finally, to test if patterns of hub scores across the brain distinguish pre-from post-treatment, we will train support-vector classifiers in a leave-one-out fashion to distinguish pre-and post-treatment conditions within each phenotype using all node hub scores. We will use permutation testing to examine the accuracy of the classifiers against 10,000 null permutations to examine the significance of our results. Further exploratory analyses will examine the specific effect of mCILT alone on language network properties.

8.4.4 Safety Analysis

All data on any and all adverse events occurring during the baseline testing, 2 week period in which tDCS is being administered, and the 12 week interval between the end of tDCS and completion of the study will be used for an overall study safety analysis.

8.5 Subject Population(s) for Analysis

The population that will be subject to analysis will be the full randomized with crossover population. Subjects that are non-compliant with treatment/crossover will be encouraged to continue with follow-up and these measurements will be enter into analysis.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

9.2 Recording of Adverse Events

At each contact with the participant, the researchers will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately to the chair of the DSMB.

9.3 *Relationship of AE to Study*

The relationship of each adverse event to the study procedures will be determined by the PI, who is a neurologist. Based on his expertise with tDCS, he will make a determination about the relationship of the adverse event to the study procedures.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.4.2 Investigator reporting: notifying the study sponsor

A serious adverse event will be reported to the IRB and chair of the DSMB by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the IRB within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

At the time of the report, the following information should be provided:

- Study Identifier
- Study Center
- Subject ID
- A description of the event
- Date of onset
- Current Status
- Whether the study treatment was discontinued
- The reason why the event is classified as serious
- PI assessment of the association between the event and study treatment

Within the following 48 hours, the investigator will provide further information on the serious adverse event in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the

event. Significant new information on ongoing serious adverse events will be provided promptly to the IRB and chair of the DSMB.

9.5 Investigator Reporting: Notifying the Penn IRB

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days. Copies of each report and documentation of DSMB/IRB notification and receipt will be kept in the Clinical Investigator's binder.

9.6 Unblinding Procedures

Participants will be told which treatment (real tDCS+CILT vs. sham tDCS+CILT) they received in what order at the completion of the entire study.

9.7 Stopping Rules

The trial maybe stopped for safety concerns or poor study performance, including failure to recruit and/or retain subjects. Subjects who report significant discomfort from tDCS, or worsening of language or cognition during tDCS will remain in the study with treatment discontinuation. Two sources of information about short-term adverse effects of tDCS on language function will be available. First, subjects and family will be asked if they see evidence of deterioration in language or other faculties each day they return for tDCS. Second, the researcher administering the mCILT will see the subject during each treatment session. S/he will be instructed to inform the PI if s/he observes a clinically significant worsening in language function. If the mCILT administrator is concerned, the WAB will be repeated. If this supports a decline from baseline (operationally defined as more than 5 points below baseline), the adverse effect will be reported and the subject will be withdrawn from treatment. In order to support the intention-to-treat analysis, all such subjects will be strongly encouraged to continue follow-up.

9.8 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.8.1 Data and Safety Monitoring Plan

Although we consider the risk to be extremely low, subject safety will assessed throughout the course of the study by asking participants if they have experienced adverse effects from the interventions. As any adverse effects of tDCS are likely to occur at the time of stimulation, we will ask all subjects during and immediately after tDCS if they note any symptoms of concern. This will be documented for each subject at each stimulation session. Risks associated with MRI, namely the accidental introduction of metal objects into the MRI suite that become projectiles or accidental scanning of subjects with ferromagnetic or programmable implants, are potentially life-threatening. However, insofar as MRI has been employed routinely in both research for many years at Penn and elsewhere and is used ubiquitously in clinical practice, there are highly robust safety precautions in place to prevent such mishaps. CAMRIS has strict monitoring procedures which will be mandated and enforced across all Penn MRI trials. It is the responsibility of the PI to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data monitoring will take place by the study staff members. We have implemented monthly checks to ensure that correct administration of the CILT is being followed. Additionally, Leslie Vnenchak – an SLP – will monitor the correct and complete collection of all language assessment data.

9.8.2 Data Safety Monitoring Board

This study will not have a DSMB. The PI will act to ensure data and safety monitoring.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

PHI (see below) as well as data from the studies to be performed during the study will be kept in an institutionally secured server, REDCap, or in a locked cabinet.
Because of our close working relationship with the FTDC, data may be shared and stored in their INDD database.

The following protected health information (PHI) will be collected:

- Name
- Age (date of birth)
- contact information (including telephone number)
- PMH (including information regarding PPA diagnosis)
- SSN
- Demographic information and results of neuroimaging.

Dr. Hamilton and the research team conducting the study will have access to the subject's PHI as well as data generated during the study. Information contained in publications and presentations will be de-identified. The Institutional Review Board (IRB) as well as the FDA and DOD may access information regarding participants should they desire. Although we will strive to protect the privacy of participants, we cannot guarantee absolute privacy.

Subjects will be contacted by the PI or a member of the study team to determine if they are interested in participating in the study. Subjects will be referred from multiple sources including colleagues at the Frontotemporal Dementia Center at Penn and UPHS physicians. Only subjects who have indicated their willingness to consider participating in the study or learn about the study will be contacted. Most potential subjects will be contacted using the phone or email script attached to this application. Subjects will interact with the PI and other members of the research team in the process of obtaining consent, during the testing before and after the treatment as well as during the administration of tDCS and mCILT.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Source documents will be kept in a secure location. Paper-based records will be kept in a locked cabinet and will only be accessible to personnel involved in the study. Most of the information will take the form of computer files; these will be de-identified by using a coding process under which subjects are identified by an assigned subject number. These files will be stored on an institutionally secured and managed device or server and/or REDCap. Because of our collaboration with Dr. Grossman and the FTDC, we may also share data back-and-forth with their group. The FTDC utilizes the INDD for data storage.

Participants will be voice and video recorded during baseline testing, mCILT treatment, and follow-up testing for the purposes of data analysis. Audio recordings will be transcribed and be saved on password-protected computers. Video recordings will be stored in an encrypted drive to be used by the study team for data coding and data analysis. All audio and video data will be stored on School of Medicine managed and secured computer devices.

10.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The PI will serve as the study monitor.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to the IRB in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All participants for this study will be provided a consent form describing this study and providing sufficient information for the participant to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a participant, using the IRB-approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form will be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.1 Risks

Potential risks of the behavioral studies, such as language assessments and speech therapy, are minimal and easily addressed with increased breaks and morale support. They include participant fatigue, boredom, or frustration.

There are well-known but rarely encountered risks from brain imaging with MRI. The risks include contrast administration (not relevant here because we will not use contrast), dislodging a metal object in the patient, interfering with an implanted device (e.g., pacemaker) and moving metallic objects in the scanner room. Protocols to deal with these issues include MRI safety screening prior to entry into the scanner. Additionally, MRI techs at HUP have metal detector wands and scan participants before entry into the MRI.

Risks from single use or repetitive (daily sessions) tDCS are well understood and appear to be minor- they are outlined below. There have been no significant side effects noted in any study involving tDCS to date. That is to say that in the approximately 300+ studies that have been published to which there have been no reported seizures, loss of consciousness or persistent neurologic signs or symptoms.

1. Mild burning sensation: One of most common adverse effect in a published review article (Kessler et al., 2012) was a mild burning sensation at the site of stimulation (that is, under the electrode). In another review, of over 527 tDCS sessions, Poreisz et al (2007) also identified a mild burning sensation in 22% of subjects.

2. Itching and/or tingling: Tied for most common adverse effects in a published review article (Kessler et al., 2012) was itching or tingling at the site of stimulation (that is, under the electrode). Poreisz et al (2007) identified this as their most common side effect with 30% of subjects reporting this experience.

3. Headache: About 10% of subjects will report headache after stimulation (Kessler et al., 2012). Symptoms are self-limiting and can be treated with over the counter medication (Tylenol, Advil).

4. Mild pain: Rarely, less than 10% of subjects will report mild pain (Poreisz et al., 2007) at the sight of stimulation.

5. Redness or soreness at the sight of the electrode: Participants with bald or shaved heads, or sensitive skin may experience some redness at the site of the electrode which will fade after stimulation stops.

Participants receiving sham stimulation can sometimes experience side effects similar to those experienced during real tDCS stimulation. This is because sham stimulation involves approximately 30 seconds of real stimulation before the machine shuts off.

tDCS is currently regarded by the Penn IRB as non-significant risk (#814366, #811842, #818622).

12.2 Adequacy of Protection Against Risks

Behavioral Studies: To protect against fatigue subjects will be permitted to rest or discontinue testing at any time. Should subjects appear to be made anxious by the tasks, testing will be terminated. Subjects will be told that they are free to withdraw from the testing at any time. The PI is not aware of any significant adverse effect from behavioral testing of the type proposed in more than 30 years of work with brain-lesion subjects.

MRI Brain Imaging: No contrast agents will be administered. The major risk from MRI is that the strong magnetic field will dislodge a metallic object inside the subject's body (e.g., aneurysm clip) or interfere with an implanted device (e.g., cardiac pacemaker). Standard protocols have been developed at the University of Pennsylvania to ensure that subjects at risk do not undergo an MRI scan. This protocol includes an extensive checklist that is completed by the subject or family member; additionally, the MRI technician interviews subjects prior to entering the MRI suite. A second potential concern comes from loose metallic objects in the MRI suite that can serve as missiles if they are drawn to a powerful magnet. Metallic objects that are not secured to the floor or wall are not permitted in the MRI suite. We note that these procedures have been employed in the clinical and research settings at the University of Pennsylvania for many years; no adverse effects from MRI scanning have been experienced to date.

Participants with a documented history of claustrophobia or known issue with participating in an MRI (i.e. anxiety) may request the use of a sedative during the scans. The PI may prescribe a mild benzodiazepine to alleviate any discomfort (i.e. claustrophobia/anxiety) caused by the MRI. For safety purposes, the participant would not be allowed to travel home alone, and would be required to have a caregiver present to provide transportation. If a caregiver is not available, transportation will be arranged for them by our research staff.

The following steps will be taken to minimize risks from tDCS identified above:

1. We will use durations and stimulus intensities that fall within parameters that have been safely used throughout tDCS research.
2. Subjects will be monitored during and after tDCS stimulation for any of the negative effects listed above. Should the subject report any adverse effects the session will be terminated. The researcher will discuss this with the PI and determine whether the participant should be withdrawn.
3. A physician will be available by phone during sessions where tDCS is being delivered.

12.3 Benefits

The objective of the study is to determine if tDCS paired with mCILT improves PPA; all subjects will crossover into the treatment group and may benefit from the treatment. We note that the study is also potentially of benefit to participants as they will receive two weeks of CILT, an accepted form of speech therapy for which there is evidence of efficacy. The study is also of potential benefit to the PPA community as it may identify an effective therapy for this disabling condition.

12.4 Risk Benefit Assessment

We believe that the investigations are likely to demonstrate that tDCS in conjunction with mCILT is beneficial for the treatment of PPA. The studies, therefore, are important as they are likely to provide evidence of efficacy for a new approach to the treatment of PPA. We believe that the potential scientific and clinical value of the information to be obtained justifies the small risk of the investigations.

12.5 Informed Consent Process / HIPAA Authorization

All subjects will be provided a consent form describing the study providing sufficient information for subjects to make an informed decision about their participation in this study. The nature and goals of the proposed research will be explained to the subjects and, as appropriate, to their families. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject or a legally acceptable surrogate must sign the consent form to participate. The Principal Investigator or study staff obtaining consent will additionally sign the form. Subjects will be consented by the study Principal Investigator, or appropriate designee, in a room we have selected in which to perform consent, which is located outside of the clinic. Potential subjects will review the consent form in detail with the person designated to consent and have the ability to take the consent home for further review. We note that the PI has worked with subjects with aphasia for more than 30 years and has extensive experience assessing the capacity of subjects with aphasia to provide and obtaining informed consent.
Since potential subjects will be recruited by phone, email or letter, and PHI will necessarily be collected to conduct screening, we will be using a verbal consent script which will be completed before any PHI is collected

13 Study Finances

13.1 Funding Source

This study will be funded through a grant obtained from the US Department of Defense (DOD).

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Subjects will be reimbursed via Greenphire ClinCard for their time at a rate of $20 per hour and their transportation costs will be paid, up to $50 per visit.

14 Publication Plan

Results of the study will be published by the PI and colleagues in peer-reviewed journals.

15 References

Agosta, F., Galantucci, S., Canu, E., Cappa, S. F., Magnani, G.,Franceschi, M., . . . Filippi, M. (2013).Disruption of structural connectivity along the dorsal and ventral language pathways in patients with nonfluent and semantic variant primary progressive aphasia: a DT MRI study and a literature review. Brain and Language, 127(2), 157-166.doi: 10.1016/j.bandl.2013.06.003

Babbitt, E., Cherney, L., & Halper, A. (2008) Measuring Communication Confidence in Persons with Aphasia. [Clinical Aphasiology Paper]

Beeson, P.M., King, R.M., Bonakdarpour, B., Henry ML, Cho H, Rapcsak SZ. (2011). Positive effects of language treatment for the logopenic variant of primary progressive aphasia. Journal of Molecular Neuroscience, 45(3), 724-36. doi: 10.1007/s12031-011-9579-2

Bindman, L. J., Lippold, O., & Redfearn, J. (1964). The action of brief polarizing currents on thecerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. The Journal of Physiology, 172(3), 369-38

Bishop, D. (1989) Test for the Reception of Grammar. [Medical Research Council]

Breier, J. I., Juranek, J., Maher, L. M., Schmadeke, S., Men, D., & Papanicolaou, A. C. (2009).Behavioral and neurophysiologic response to therapy for chronic aphasia. Archives of Physical Medicine and Rehabilitation, 90(12),2026-2033.doi: 10.1016/j.apmr.2009.08.144

Boyle, M. (2004). Semantic feature analysis treatment for anomia in two fluent aphasia syndromes. American Journal of Speech-Language Pathology, 13(3), 236-249.doi: 10.1044/1058-0360(2004/025

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., . . . Johnson, K. A. (2009).Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, andrelation to Alzheimer's disease. Journal of Neuroscience, 29(6), 1860-1873.doi:10.1523/JNEUROSCI.5062-08.2009

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.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. doi:10.1080/02687030801943179

Croot, K., Taylor, C., Abel, S., Jones, K., Krein, L., Hameister, I., . . . 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.doi:10.1080/02687038.2014.975181

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato,D., & Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimulation, 2(4), 201-207.

de Aguiar, V., Bastiaanse, R., Capasso, R., Gandolfi, M., Smania, N., Rossi, G., & Miceli, G. (2015).Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs? Frontiers in Behavioral Neuroscience, 9, 1-17.doi:10.3389/fnbeh.2015.00190

Diehl-Schmid, J., Schmidt, E. M., Nunnemann, S., Riedl, L., Kurz, A., Forstl, H., . . . Cramer, B. (2013). Caregiver burden and needs in frontotemporal dementia. Journal of Geriatric Psychiatry and Neurology, 26(4), 221-229. doi:10.1177/0891988713498467

DSI Studio. (2013). Retrieved September 27, 2017, from http://dsi-studio.labsolver.org/

Elman, R. J., & Bernstein-Ellis, E. (1999). The efficacy of group communication treatment in

adults with chronic aphasia. Journal of Speech Language and Hearing Research,42(2).doi:10.1044/jslhr.4202.411

Engels, M. M., Stam, C. J., van der Flier, W. M., Scheltens, P., de Waal, H., & van Straaten, E. C.(2015). Declining functional connectivity and changing hub locations in Alzheimer's disease: an EEG study. BMC Neurology,15, 145. doi:10.1186/s12883-015-0400-7

Dell, G.S., Martin, N., & Schwartz, M.F. (2007). A case-series test of the interactive two-step model of lexical access: Predicting word repetition from picture naming. Journal of Memory and Language. 56, 490-520

Fornito, A., &Bullmore, E. T. (2015). Reconciling abnormalities of brain network structure and function in schizophrenia. Current Opinion in Neurobiology, 30, 44-50. doi:10.1016/j.conb.2014.08.006

Friel, K. M., Lee, P., Soles, L. V., Smorenburg, A. R., Kuo, H.-C., & Edwards, D. J. (2017). Combined transcranial Direct Current Stimulation and robotic upper limb therapy improves upper limb function in an adult with cerebral palsy. NeuroRehabilitation (Preprint), 1-10.doi: 10.3233/NRE-171455

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

Giannini, L. A., Irwin, D. J., McMillan, C. T., Ash, S., Rascovsky, K., Wolk, D. A., . . . Grossman, M.(2017). Clinical marker for Alzheimer disease pathology in logopenic primary progressive aphasia. Neurology, 88(24), 2276-2284.doi: 10.1212/WNL.0000000000004034

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),1006–1014.doi: 10.1212/WNL.0b013e31821103e6

Grossman, M. (2010). Primary progressive aphasia: Clinicopathological correlations. Nature Reviews Neurology, 6(2). doi:10.1038/nrneurol.2009.216

Grossman, M. (2012). The non-fluent/agrammatic variant of primary progressive aphasia. The Lancet Neurology, 11(6), 545-555.doi:10.1016/S1474-4422(12)70099-6

Grossman, M. 2018. Linguistic aspects of primary progressive aphasia. Annual Review of Linguistics,4, 377-403, 2018. doi.org/10.1146/annurev-linguistics-011516-034253

Hameister, I., Nickels, L., Abel, S., Croot, K. (2017). “Do you have mowing the lawn?”– improvements in word retrieval and grammar following constraint-induced language therapy in primary progressive aphasia.Aphasiology,31(3), 308-331.doi:10.1080 /02687038.2016.1197558

Hashimoto, N., & Frome, A. (2011). The use of a modified semantic features analysis approach in aphasia. Journal of Communication Disorders, 44(4), 459-469.doi:10.1016/ j.jcomdis. 2011.02.004

Henry, M. L., Beeson, P. M., & Rapcsak, S. Z. (2008). Treatment for lexical retrieval in progressive aphasia. Aphasiology, 22(7-8), 826-838. doi:10.1080/02687030701820055

Henry, M. L., Meese, M. V., Truong, S., Babiak, M. C., Miller, B. L., & Gorno-Tempini, M. L. (2013a).Treatment for apraxia of speech in nonfluent variant primary progressive aphasia. Behavioural Neurology, 26(1-2), 77-88.doi: 10.3233/BEN-2012-120260

Henry, M. L., Rising, K., DeMarco, A. T., Miller, B. L., Gorno-Tempini, M. L., & Beeson, P. M. (2013b). Examining the value of lexical retrieval treatment in primary progressive aphasia: Two positive cases. Brain and Language, 127(2), 145-156.doi: 10.1016/j.bandl.2013.05.018

Henry, M. L., Wilson, S. M., Babiak, M. C., Mandelli, M. L., Beeson, P. M., Miller, Z. A., &

Gorno-Tempini, M. L. (2016). Phonological processing in primary progressive aphasia. Journal of Cognitive Neuroscience, 28(2), 210-222.doi: 10.1162/jocn_a_00901

Howard, D., Patterson, K. E., & Company, T. V. T. (1992). The Pyramids and Palm Trees Test: A Test of Semantic Access from Words and Pictures: Thames Valley Test Company.

Hung, J., Bauer, A., Grossman, M., Hamilton, R. H., Coslett, H., & Reilly, J. (2017). Semantic Feature Training in Combination with Transcranial Direct Current Stimulation (tDCS) for Progressive Anomia. Frontiers in Human Neuroscience, 11.doi:10.3389/ fnhum. 2017. 00253

Jackson, M. P., Rahman, A., Lafon, B., Kronberg, G., Ling, D., Parra, L. C., & Bikson, M. (2016). Animal models of transcranial direct current stimulation: Methods and mechanisms. ClinicalNeurophysiology, 127(11), 3425-3454.doi: 10.1016/j.clinph.2016.08.016

Jokel, R., Graham, N. L., Rochon, E., & Leonard, C. (2014). Word retrieval therapies in primary progressive aphasia. Aphasiology, 28(8-9), 1038-1068. doi:10.1080/02687038.2014. 899306

Maher, L. M., Kendall, D., Swearengi n, J. A., Rodriguez, A., Leon, S. A., Pingel, K., . . . Rothi, L. J. G.(2006). A pilot study of use-dependent learning in the context of constraint induced language therapy. Journal of the International Neuropsychological Society, 12(6), 843-852.doi.org/10.1017/S1355617706061029

McConathey, E. M., White, N. C., Gervits, F., Ash, S., Coslett, H. B., Grossman, M., & Hamilton, R. H.(2017). Baseline performance predicts tDCS-mediated improvements in language symptoms in primary progressive aphasia. Frontiers in Human Neuroscience, 11. doi:10.3389/fnhum.2017.00347

Mesulam,M.-M.(2001). Primary progressive aphasia. Annals of Neurology 49(4),425–32.doi:10.1007/s00115-004-1770-z

Mesulam, M.M., Rogalski, E.J., Wieneke, C., Hurley, R.S., Geula, C., Bigio, E.H., Thompson, C.K., &Weintraub, S. (2014) Primary progressive aphasia and the evolving neurology of the language network. Nature Reviews Neurology 10, 554-69. doi: 10.1038/nrneurol.2014.159

Mioshi, E., Bristow, M., Cook, R., & Hodges, J. R. (2009). Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. Dementia and Geriatric Cognitive Disorders,27(1), 76-81. doi:10.1159/000193626

Mioshi, E., Foxe, D., Leslie, F., Savage, S., Hsieh, S., Miller, L., . . . Piguet, O. (2013). The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. Alzheimer Disease & Associated Disorders, 27(1), 68-73.doi:10.1097/WAD.0b013e318247a0bc

Mortensen, J., Figlewski, K., & Andersen, H. (2016). Combined transcranial direct current stimulation and home-based occupational therapy for upper limb motor impairment following intracerebral hemorrhage: a double-blind randomized controlled trial. Disability and Rehabilitation, 38(7), 637-643.doi:10.3109/09638288.2015.1055379

National Alzheimer's Coordinating Center. (2010). FTLD Module v3 forms and documentation. Retrieved July 19, 2017, fromhttps://www.alz.washington.edu/WEB/forms_ftld.html

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . Fregni, F. (2008).Transcranial direct current stimulation: state of the art 2008.Brain Stimulation, 1(3), 206-223. doi:10.1016/j.brs.2008.06.004

Nitsche, M. A.,Liebetanz, D., Lang, N., Antal, A., Tergau, F., Paulus, W. (2003). Safety criteria fortranscranial direct current stimulation (tDCS) in humans.Clinical Neurophysiology, 114, 2220-2222.

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.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology, 527(3), 633-639.doi:10.1111/j.1469-7793.2000.t01-1-00633.x

Norise, C., & Hamilton, R. H. (2017). Non-invasive brain stimulation in the treatment of post-stroke and neurodegenerative aphasia: Parallels, differences, and lessons learned. Frontiers in Human Neuroscience, 10.doi: 10.3389/fnhum.2016.00675

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. Frontiers in Human Neuroscience, 11.doi:10.3389/fnhum.2017.00260

Page, S. J., Cunningham, D. A., Plow, E., & Blazak, B. (2015). It takes two: noninvasive brain stimulation combined with neurorehabilitation. Archives of Physical Medicine and Rehabilitation,96(4), S89-S93.doi: 10.1016/j.apmr.2014.09.019

Price, A. R., McAdams, H., Grossman, M., & Hamilton, R. H. (2015). A meta-analysis of transcranial direct current stimulation studies examining the reliability of effects on language measures. Brain Stimulation, 8(6), 1093-1100.doi: 10.1016/j.brs.2015.06.013

Price, A. R., Peelle, J. E., Bonner, M. F., Grossman, M., &Hamilton, R. H. (2016). Causal evidence fora mechanism of semantic integration in the angular gyrus as revealed by high-definition transcranial direct current stimulation. The Journal of Neuroscience, 36(13), 3829-3838.doi:10.1523/jneurosci.3120-15.2016

Kessler, S.K., Turkeltaub, P.E., Benson, J.G., & Hamilton, R.H. (2012). Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimulation, 5 (2), 155-162.

Pulvermüller, F., Neininger, B., Elbert, T., Mohr, B.,Rockstroh, B., Koebbel, P., & Taub, E. (2001).Constraint-induced therapy of chronic aphasia after stroke. Stroke, 32(7), 1621-1626.doi:10.1161/01.STR.32.7.1621

Poreisz, C., Boros, K., Antal, A. & Paulus, W. (2007). Safety aspects of trancranial direct current stimulation concerning healthy subjects and patients. Brain Research Bulletin, 72 (4-6), 208-214.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., & Bikson, M. (2013). Cellulare ffects of acute direct current stimulation: somatic and synaptic terminal effects. The Journal of Physiology, 591(10), 2563-2578.doi: 10.1113/jphysiol.2012.247171

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013). Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Frontiers in Human Neuroscience, 7.doi: 10.3389/fnhum.2013.00687

Riedijk, S.R., De Vugt, M. E., Duivenvoorden, H. J., Niermeijer, M. F., Van Swieten, J. C., Verhey, F.R., & Tibben, A. (2006). Caregiver burden, health-related quality of life and coping in dementiacaregivers: a comparison of frontotemporal dementia and Alzheimer's disease. Dement GeriatrCogn Disord, 22(5-6), 405-412. doi:10.1159/000095750

Ruf, S. P., Fallgatter, A. J., & Plewnia, C. (2017). Augmentation of working memory training by transcranial direct current stimulation (tDCS).Scientific Reports, 7(1), 876.doi: 10.1038/s41598-017-01055-1

Shah-Basak, P. P., Wurzman, R., Purcell, J. B., Gervits, F., & Hamilton, R. (2016). Fields or flow? A comparative metaanlysis of transcranial magnetic and direct current stimulation to treat post-stroke aphasia. Restorative neurology and neuroscience, 34(4), 537-559.

Shewan, C. M., & Kertesz, A. (1980). Reliability and validity characteristics of the Western Aphasia Battery (WAB). Journal of Speech and Hearing Disorders, 45(3), 308-324.

Sporns, O., Chialvo, D., Kaiser, M., & Hilgetag, C. (2004). Organization, development and function of complex brain networks. Trends in Cognitive Sciences, 8(9), 418-425.doi:10.1016/j.tics.2004.07.008

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

Stam, C. J. (2014). Modern network science of neurological disorders. Nature Reviews Neuroscience,15(10), 683.doi:10.1038/nrn3801

Sobel, P., Brecher, A. & Schwartz, M.F. (2006). Nonword Repetition Test based on the PNT. Unpublished test.

Stark, J. A. (2010). Content analysis of the fairy tale Cinderella – A longitudinal single-case study of narrative production: "From rags to riches", Aphasiology, 24(6), 709-724.

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

Turkeltaub, P. E., Benson, J., Hamilton, R. H., Datta, A., Bikson, M., & Coslett, H. B. (2012). Left lateralizing transcranial direct current stimulation improves reading efficiency. Brain Stimulation,5(3), 201-207.doi: 10.1016/j.brs.2011.04.002

Wang, H., Suh, J.W., Das, S.R., Pluta, J.B., Craige, C., & Yushkevich, P.A. (2013) Multi-Atlas Segmentation with Joint Label Fusion. EEE Trans Pattern Anal Mach Intell, 35(3), 611-23. doi:10.1109/TPAMI.2012.143

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. Neuroscience Letters, 549, 29-33.doi:10.1016/j.neulet.2013.06.019

16 Attachments

- Sample Consent Form
- Study Procedures Flowchart
- Inclusion/Exclusion Form
- MRI Safety Screening
- Daily tDCS Log
- mCILT Manual

17 Appendix

17.1 tDCS_NeuroConn Manual