

**AWARD NUMBER:** W81XWH-20-1-0490

**TITLE:** 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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**CONTRACTING ORGANIZATION:** University of Pennsylvania, Philadelphia, PA

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**TYPE OF REPORT:** Annual

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Primary Progressive Aphasia, or PPA, is a condition that affects language abilities. A person with PPA may have difficulties speaking, understanding speech, reading, or writing, and these difficulties worsen over time. The purpose of this study is to determine whether a form of non-invasive brain stimulation called Transcranial Direct Current Stimulation (or tDCS) can be used as a therapeutic technique, in combination with Constraint-Induced Language Therapy (CILT), to improve the language symptoms of PPA. This is a double-blind, randomized, crossover study.					
<b>15. SUBJECT TERMS</b>					
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## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	5
2. Keywords	5
3. Accomplishments	6
4. Impact	8
5. Changes/Problems	8
6. Products	10
7. Participants & Other Collaborating Organizations	10
8. Special Reporting Requirements	11
9. Appendices	11

## 1. INTRODUCTION:

Primary progressive aphasia (PPA) is a debilitating condition associated with focal degeneration of the language-dominant left hemisphere of the brain. Two PPA variants—nonfluent/agrammatic (naPPA) and semantic variant (svPPA)—together affect up to 40% of patients with frontotemporal degeneration (FTD). While there are currently no treatments that reverse or significantly slow the progression of PPA, a small body of evidence suggests that combining transcranial direct current stimulation (tDCS), a form of noninvasive neuromodulation, with behavioral language therapy may hold out promise. In addition, recent advances in network science, specifically the ability to characterize the function of critical centers of connectivity (or hubs) in the language network, may enhance understanding of how both neurodegeneration and tDCS impact language network functions and consequently communication ability. The objectives of this proposal are to further develop tDCS as a novel clinical intervention for FTD-associated PPAs and to employ network neuroscience tools in order to elucidate both the neural underpinnings of aphasia symptoms in PPA and the mechanisms by which tDCS may enhance language performance in these disorders. The project is comprised of a randomized, double-blind, sham-controlled, two-armed crossover study in which subjects with naPPA and svPPA will undergo language testing and structural (MPRAGE, DSI) and functional brain imaging (IFC) before and after receiving 10 sessions (Mon-Fri x 2 weeks) of real tDCS (20 min x 1.5mA; anode=F7, cathode = O1; 5cm x 5cm electrode pads) or sham tDCS paired with mCILT. Language testing and brain imaging will be repeated immediately after completion of and 3 months following the end of treatment. The primary outcome measure will be the WAB-AQ; additional standardized language instruments will serve as secondary outcome measures, as will the performance on trained and untrained stimulus items employed during mCILT training.

## 2. KEYWORDS:

Primary progressive aphasia  
Transcranial direct current stimulation  
Constraint induced language therapy  
Dementia  
Noninvasive brain stimulation  
Frontotemporal dementia  
Network neuroscience

### 3. ACCOMPLISHMENTS:

#### What were the major goals of the project?

The major goals of the project for this reporting period, which were outlined and approved in our SOW document, are outlined in the table below.

	Timeline	% completed
<b>Major Task 1: Prepare Regulatory Documents and Research Protocol</b>		
	Months	
Finalization and approval of final IRB Protocol and IC form at PENN	1-2	100%
IRB protocol approval at coordinating sites (VAMC only)	1-3	0%
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	1-4	100%
Coordinate with sites for annual IRB report for continuing review	Yearly	100%
Submit amendments, adverse events, and protocol deviations as needed	As needed	100%
<i>Milestone Achieved: IRB Approval at Penn</i>	3	100%
<i>Milestone Achieved: HRPO approval for protocols</i>	4	100%
<i>Milestone Achieved: IRB approval at all sites</i>	4	75%
<b>Major Task 2: Coordinate Study Staff</b>		
Interview and hire study staff	Pre-award	100%
Complete staff training regarding tDCS procedures, data collection, scoring	Pre-award	100%
Complete training of study staff on mCILT protocol procedures	1-3	100%
Develop and update study procedures manual for future study staff	3-36	100%
Refresh staff training on mCILT protocol and testing procedures	Yearly	100%
<i>Milestone Achieved: Staff trained on all protocol procedures</i>	3	100%
<i>Milestone Achieved: High level of staff training on procedures maintained</i>	3-32	100%
<b>Major Task 3: Participant Recruitment, Intervention, and Data Collection</b>		
Initiate subject recruitment	4	100%
Participants complete 1st assigned condition, cross over, and complete 2nd assigned condition	4-28	4.8%
Participants complete follow-up assessments 12 weeks after completion of the intervention	7-32	3.2%
<i>Milestone Achieved: 1<sup>st</sup> participant consented, screened and enrolled</i>	4	100%

## **What was accomplished under these goals?**

During this reporting period, we were able to accomplish the majority of the study activities outlined in our SOW for completion in the first two years (24 months). However, we continue to struggle with obtaining IRB approval from the Corporal Michael J. Crescenz Veterans Affairs Medical Center (CMCVAMC), our VAMC coordinating site. We have reached out to the VAMC multiple times for guidance on submitting a reliance agreement with Penn as the IRB of record but have not received a reply. Consequently, no study activity has taken place at the VAMC to date. We will continue to work with Penn's IRB and the VAMC to resolve this issue and anticipate addressing this issue with research leadership in the CMCVIAMC Medical Research Program, including but not limited to members of the CMCVAMC R&D Committee. Please consider that anticipated enrollment from the VAMC was only predicted to be 5 participants over the course of the entire study, so this delay should not greatly effect reaching our recruitment goals.

The main goal for study progress outlined in our SOW for this year was to recruit participants and collect data. In the past 12 months we have made considerable effort to increase enrollments. The hesitance to participate that we initially experienced from potential subjects earlier in the pandemic has largely subsided, and University regulations surrounding COVID-19 prevention have been lifted. We have also increased the number of research assistants working on this study in an effort to increase our capacity to enroll and run subjects. Our new study team has enrolled 9 participants in the past 12 months. We currently have 11 participants enrolled: 2 did not qualify due to medical issues, 2 has completed the study, 1 is awaiting the 24 week follow-up, 4 are in Arm 1 follow-up, 0 is in Arm 2 treatment, 1 is undergoing baseline testing and 1 has withdrawn.

Although we have made great progress in the past 12 months, we continue to fall behind our anticipated target enrollments. We currently have 127 subjects that have expressed interest in participating, of those 11 passed the phone screening and are awaiting enrollment, 72 failed the phone screen and were deemed to not qualify, and 33 are awaiting to be contacted (see Figure 1).

## **What opportunities for training and professional development has the project provided?**

Nothing to report.

## **How were the results disseminated to communities of interest?**

Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

We recognize that multiple factors including but not solely limited to the COVID pandemic have put our team behind schedule with respect to the completion of study enrollment and subsequent data analysis, which we had originally anticipated would happen in the next reporting period. Therefore, our major goal for the next reporting period is to focus on maximizing our recruitment and enrollment numbers. We believe that our two newly hired research assistants have and will continue to accelerate study enrollment. Additionally, we strongly believe that expanding our participant pool to include those with the logopenic variant of PPA (lvPPA), a far more common variant, will increase our enrollment numbers. The inclusion of individuals with lvPPA had added an additional 50 to our participant pool.

**4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

*Nothing to report.*

**What was the impact on other disciplines?**

*Nothing to report.*

**What was the impact on technology transfer?**

*Nothing to report.*

**What was the impact on society beyond science and technology?**

*Nothing to report.*

**5. CHANGES/PROBLEMS:**

There have been seven protocol deviations. On 8/30/2021, upon routine data review, it was discovered that dPPA-01 did not receive two administrations of the WAB and CILT at the 12 week crossover baseline. On 1/31/2022, upon routine data review, it was discovered that dPPA-01 received an MRI at the 24 week time-point. On 1/31/2022, it was reported that dPPA-05 would have two sets of baseline testing due to too large of time lag between baseline and treatment. On 2/4/2022, it was reported that dPPA-04 would only have 9 treatment sessions for Arm 2 due to illness. On 2/23/22, it was reported that dPPA-05 had to finish baseline testing directly before treatment because of time constraints. On 2/28/22, it was reported that dPPA-05 did not receive Day 3 Arm 1 treatment because of behavioral issues (touching and moving the tDCS electrodes). On 5/10/2022, it was

reported that dPPA-09 would complete their immediate follow-up MRI at the 6 week follow-up due to out-of-state travel.

There have been 5 adverse events. The first occurred on the evening of 2/5/2022, dPPA-04 reported a headache which occurred over the weekend between Arm 2 treatment. The headache lasted for about 1 hour and was treated at home with Tylenol. Due to the timing of the event, >24 hours after treatment, we do not believe this is related to study treatment. On 2/14/2022, dPPA-04 reported skin irritation on their forehead which began after Arm 2 treatment and lasted for the day but went away on its own. Skin irritation is a known side-effect of tDCS and the participant remained willing to participate. On 2/23/2022, dPPA-05 experienced mild skin irritation under the electrode during Arm 1 Day 3 treatment. We believe the irritation was caused by behavioral issues exhibited by the participant on that day which included touching, rubbing, and trying to dry the electrode sponges. Day 3 treatment was discontinued but the subject remained willing to participate. On 3/24/2022, at the Arm 2 6 week follow-up, dPPA-04 reported daily headaches for the past 2 weeks that would go away after taking ibuprofen. Since the headaches began 4 weeks after treatment ended, we do not think they are related to treatment. Lastly on 5/26/2022, dPPA-10 complained of chest pain and was escorted to the ER by a research assistant. After being seen, it was determined it was an episode of acid reflux or GERD and the patient was discharged that same day. This AE took place 40 minutes after treatment, but was deemed to be unrelated due to the nature of the event.

### **Changes in approach and reasons for change**

Two main modifications were made to the protocol during this reporting period which altered our approach for recruitment and testing. Firstly, we are now enrolling participants with lvPPA. This is a far more common PPA subtype and has allowed us to increase our outreach and not turn away interested individuals. Secondly, we made the option for virtual enrollment/testing a permanent option which has greatly helped potential subjects who travel long distances for our study. The option for virtual testing has been a major selling point for many of our participants and we believe will help increase enrollment and reduce attrition.

### **Actual or anticipated problems or delays and actions or plans to resolve them**

We have not yet received IRB approval from the Corporal Michael J. Crescenz Veterans Affairs Medical Center. We are continuing to work with Penn's IRB and the VAMC to resolve this issue. However, it is important to note that the anticipated study recruitment at the Corporal Michael J. Crescenz VAMC represents a small fraction of the total recruitment of the study

Another challenge has been employee turnover. The research assistant associated with this study left their position on June 17, 2022, which forced us to delay new enrollments in the month of July. However, we were able to fill the position July 1, 2022 and have begun training. We are also in the process of hiring a second RA who we anticipate will start in August 1, 2022.

**Changes that had a significant impact on expenditures**

Nothing to report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

**6. PRODUCTS:**

Nothing to report.

**7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Roy H. Hamilton, No change.  
H. Branch Coslett, No change.  
Daniela Sacchetti, No change.  
Denise Harvey, No change.  
Leslie Vnenchak, No change.  
Olufunso Fasyeitán, No change.  
Taylor Phillips, No change.

Name:	<i>Suravi Sakar</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	1 person months
Contribution to Project:	Trained on study procedures. Begun recruitment identification process.
Funding Support:	DoD CDMRP FY19 PRMRP (Award #: W81XWH-20-1-0490)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

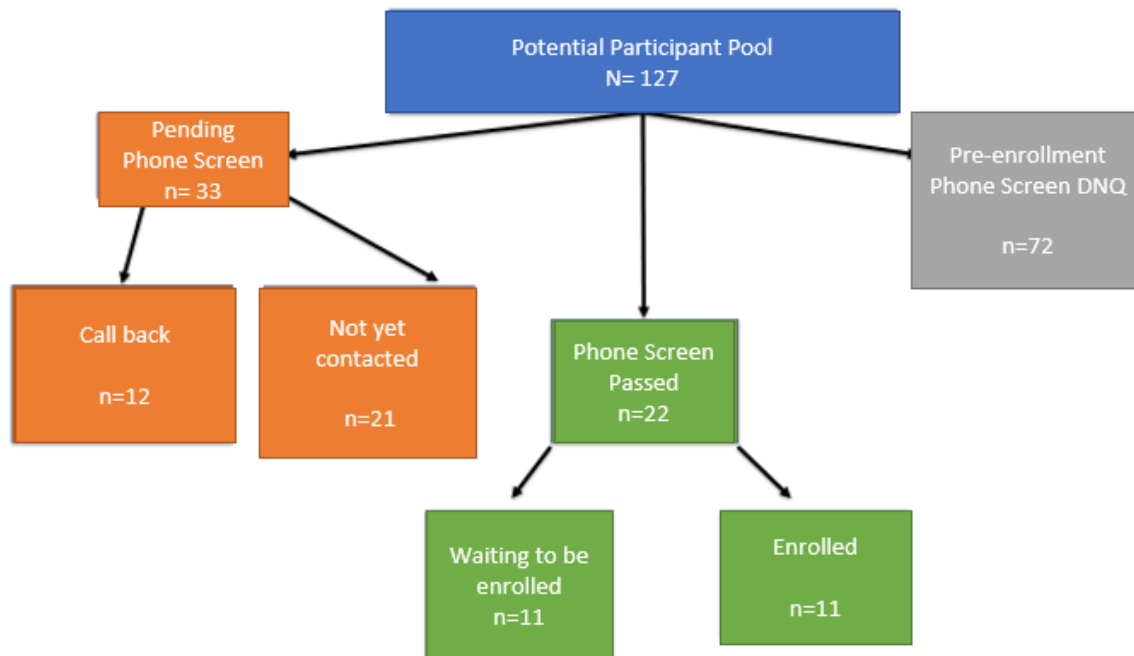
Nothing to report.

### 8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

### 9. APPENDICES:

Figure 1: Recruitment Breakdown



**Table 1: Reason for Phone Screen Failures**

<b>Reason</b>	<b>Number</b>	<b>Percentage</b>
Age out of range	4	5.5%
MMSE/AD Diagnosis	1	1.3%
Doesn't have PPA Dx	10	13.8%
Non-native English speaker	6	8.3%
Too Impaired	5	6.9%
Poor Health	1	1.3%
Not able to travel to treatment site	9	12.5%
Too much time commitment	7	9.7%
Stroke	4	5.5%
Small Vessel Ischemic Disease	2	2.7%
Unable to contact/No longer interested	20	27.7%
Deceased at point of contact	3	4.2%
<b>Total Screen Failures</b>	72	76.6%
<b>Total Screened</b>	94	