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

**PRINCIPAL INVESTIGATOR:** Roy H. Hamilton, MD, MS

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

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**14. ABSTRACT**

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.

**15. SUBJECT TERMS**

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

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
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## 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 |
|---|---|---|
| **Major Task 1: Prepare Regulatory Documents and Research Protocol** | 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% |
| *Milestone Achieved: IRB Approval at Penn* | 3 | 100% |
| *Milestone Achieved: HRPO approval for protocols* | 4 | 100% |
| *Milestone Achieved: IRB approval at all sites* | 4 | 75% |
| **Major Task 2: Coordinate Study Staff** | | |
| 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% |
| *Milestone Achieved: Staff trained on all protocol procedures* | 3 | 100% |
| *Milestone Achieved: High level or staff training on procedures maintained* | 3-32 | 100% |
| **Major Task 3: Participant Recruitment, Intervention, and Data Collection** | | |
| Initiate subject recruitment | 4 | 100% |
| *Milestone Achieved: 1st participant consented, screened and enrolled* | 4 | 100% |
| Participants complete 1st assigned condition, cross over, and complete 2nd assigned condition | 4-28 | 22.5% |
| Participants complete follow-up assessments 12 weeks after completion of the intervention | 7-32 | 14.5% |
| **Major Task 3: Data Analysis** | | |
| Perform analysis of all behavioral data, including language assessments (Aim 1) | 28-32 | 0% |
| Perform analysis of all structural and functional imaging data (Aims 2 & 3) | 28-32 | 0% |
| Develop statistical model of response to tDCS (Aim 4) | 28-32 | 0% |

| | | |
|---|---|---|
| *Milestone Achieved: Complete all data analyses* | 32 | 0% |
| **Major Task 4: Results Reporting** | | |
| Report results of all behavioral data, including language assessments (Aim 1) | 32-36 | 0% |
| Report results of all structural and functional imaging data (Aims 2 & 3) | 32-36 | 0% |
| Report results of statistical model of response to tDCS (Aim 4) | 32-36 | 0% |
| *Milestone Achieved: Complete all data analyses* | 36 | 0% |

**What was accomplished under these goals?**

While we have been able to accomplish many of the study activities outlined in our SOW for completion in the first two years (24 months), we have continued to lag with respect to achieving our target enrollment. We have therefore extended our study recruitment period rather than proceeding to the tasks originally outlined for Year 3 involving data analysis and results reporting. Correspondingly, we have requested and received approval for a No-Cost Extension (NCE) which extends our timeline by another year.

In the past year, our study team continues to make considerable effort to increase enrollments. We have enrolled 10 participants in the past 12 months. We currently have 21 participants enrolled: 3 did not qualify due to medical issues, 7 have completed the study, 1 is awaiting the 24-week follow-up, 1 is awaiting Arm 2 treatment, 5 are in Arm 2 follow-up, 3 have dropped-out, and 1 was lost to follow up.

We have made significant progress with respect to recruitment and testing in the earlier half of the reporting period. As we previously reported, we have increased our research staff in order to enable increased recruitment and testing; in total, we have hired five new RA's this period. In addition, new staff has helped to carve out several outreach measures including directly reaching out to neurologists in the Philadelphia area and sending physical copies of our study recruitment materials to speech-language pathology practices and neurology clinics in the Greater Philadelphia area. We also send periodic recruitment emails to Primary Progressive Aphasia support groups and have joined the National Aphasia Association's PPA task force. We have also increased diversity outreach by making growing efforts to partner with organizations in the West Philadelphia community and attend several outreach events. A recent notable example was a large Juneteenth Wellness Summit held in West Philadelphia, where members of the team provided education about healthy brain aging, aphasia, PPA, and information on our studies. Looking forward we anticipate building stronger relationships with existing community members with recent appointment of an RA whose primary responsibility will be outreach.

Looking forward, we currently have 62 participants in our pipeline for future recruitment (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?**

Our major goal for the final reporting period is to increase our recruitment and enrollment numbers and continue data collection. We have continued to see an overall increase in our subject recruitment relatively to the rate of recruitment we observed in the first year of the project—January 2021 to January 2022—during the long wake of the COVID pandemic (Figure 4). We attribute this improvement to both an increase in subjects' comfort in participating in research in the wake of the COVID pandemic, as well as the inclusion of persons with lvPPA into our participant pool. We anticipate that these changes, the addition of several new research coordinators, and our increased outreach efforts to patient advocacy groups and caregivers (see above) will enable us to maximize our recruitment during the the no-cost extension period.

## *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 has been four protocol deviations. On September 26, 2022 during Arm 1 - 6 day treatment, dPPA-12 was given tDCS stimulation using incorrectly sized electrodes. The

research assistant accidentally used 5x7 electrodes instead of 5x5. It is possible that the larger electrode would stimulate a larger area of brain, which could affect scientific integrity. However, we do not believe that this one time error will have any major effect in the data. We will make a note and consider this if the data analysis shows outliers.
On January 5, 2023 another deviation was identified that occurred on 11/28/22 with dPPA-15's baseline testing. We used their baseline testing data collected from a different protocol with the same testing battery. This decision was made to reduce participant burden of having to repeat testing they already completed.
On February 6, 2023 dPPA-17 only received 9 days of Arm 1 treatment due to machine malfunction. It is possible that missing 1 day of treatment could affect the overall treatment effect; however, highly unlikely. We will flag this data as a potential outlier in our analysis.
On February 13, 2023 a long standing deviation was identified which occurred between 09/15/22-02/13/23 and affected 7 participants. During routine RA training, it was discovered that staff were inverting tDCS electrode placement and switching placement of the cathode and anode during some treatment sessions. Although the switching of the electrode isn't a major data integrity issue because the current flow is still throughout the intended brain region, combining this data with data that uses the intended montage will not be justifiable. This deviation was reported & acknowledged by our program officer and HPRO.

There have been 5 adverse events. The first occurred on 8/22/22, the participant suffered a fall with subsequent hospitalization. dPPA-05 passed out in her kitchen and hit her head. She was seen in the ER and they ruled out any issues. They suspected dehydration. The cut was stitched and she was sent home without issue. Since this fall occurred at home sometime between 6 week and 12 week follow-up testing, we do not believe this was related to study activity. The second occurred 917/2022, dPPA-14 fell at their home. They were taken to the Hospital and treated for a black eye and cut on her forehead. The participant was sent home with no other issues. Since the event occurred at home after Arm 1 baseline testing we do not believe this was related to any study activity. dPPA-14 suffered another fall at home which we were alerted about on January 6, 2023. They fractured their right ulna and wrist. This participant was lost to follow-up after release from rehab. Since the event occurred at home after Arm 1 baseline testing we do not believe this was related to any study activity. On January 24, 2023, upon her walk home from Arm 2 Day 1 treatment dPPA-13 tripped and fell on the sidewalk resulting to damage to her 2 front teeth. She also reported a mild headache following the fall which cleared the next day on its own. dPPA-13 saw their dentist and received treatment for her teeth. We believe this AE is unrelated to the treatment because the fall and headache were a direct result of tripping on the sidewalk. Lastly, on January 31, 2023 we were notified that dPPA-19 was receiving hip replacement surgery. This AE was unrelated to treatment because the participant had not even completed baseline testing yet.

**Changes in approach and reasons for change**

There were no major modifications made this reporting period. We did submit multiple personnel modifications to update study staff to include new hires.

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

We have been unable to obtain IRB approval from the Corporal Michael J. Crescenz Veterans Affairs Medical Center (CMCVAMC), our VAMC coordinating site. After reaching out to the VAMC multiple times for guidance on submitting a reliance agreement with Penn as the IRB of record with no reply we have decided to forgo this effort. Consequently, no study activity has taken place at the VAMC to date; however, anticipated enrollment from the VAMC was only predicted to be 5 participants over the course of the entire study, so this loss should not greatly effect reaching our recruitment goals.

**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 Faseyitan, No change.
Taylor Phillips, No change.
Suravi Sakar, No change.
Rishi Vas, No change.
Kayla Alznauer, No change.
Megan Hoffman, No change.

| | |
|---|---|
| Name: | *Benjamin Murdoch* |
| Project Role: | *Research Assistant* |
| Researcher Identifier (e.g. ORCID ID): | *N/A* |
| Nearest person month worked: | 1 person months |
| Contribution to Project: | Currently training on study procedures. Begun recruitment identification process. |
| Funding Support: | DoD CDMRP FY19 PRMRP (Award #: W81XWH-20-1-0490) |

| | |
|---|---|
| Name: | *Jeffry Alfaro* |
| Project Role: | *Research Assistant* |
| Researcher Identifier (e.g. ORCID ID): | *N/A* |
| Nearest person month worked: | 1 person months |
| Contribution to Project: | Currently training 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

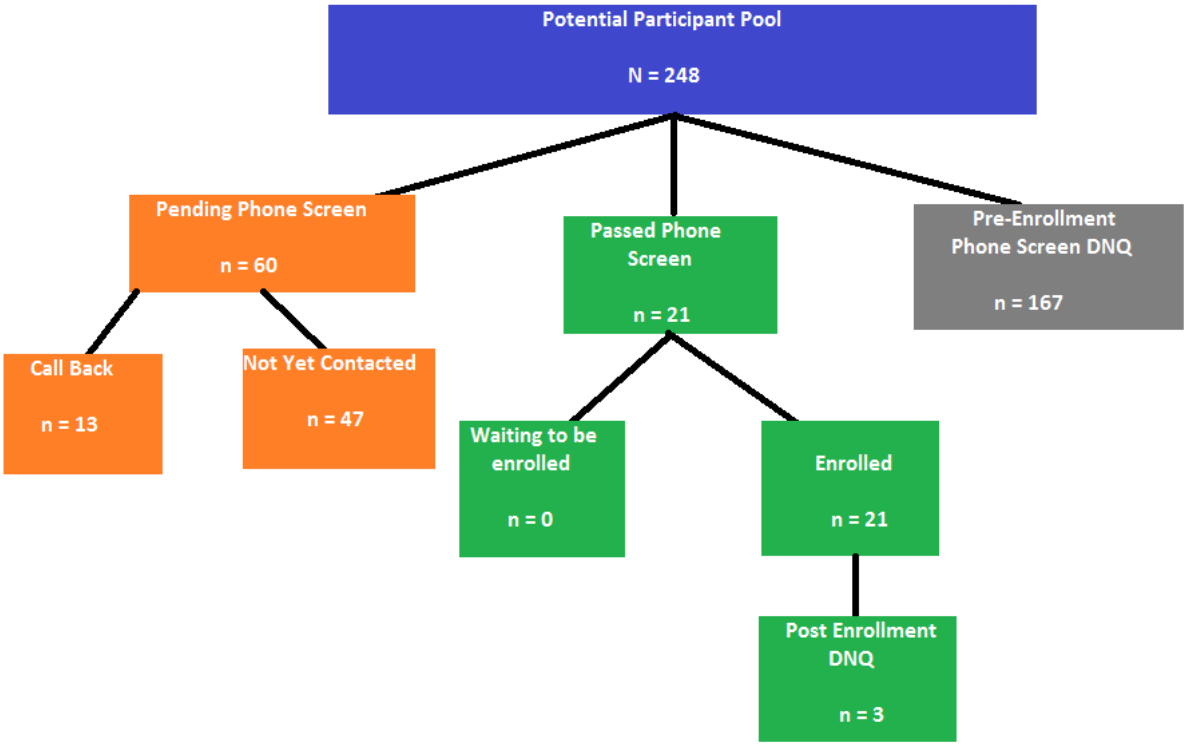

**Table 1: Reason for Phone Screen Failures**

| Reason | Number | Percentage |
|---|---|---|
| Age out of range | 13 | 7.8% |
| MMSE/AD Diagnosis | 17 | 10.1% |
| Doesn't have PPA Dx | 13 | 7.8% |
| Non-native English speaker | 9 | 5.3% |
| Too Impaired | 18 | 10.7% |
| Poor Health | 2 | 1.2% |
| Not able to travel to treatment site | 13 | 7.8% |
| Too much time commitment | 9 | 5.3% |
| Stroke | 4 | 2.4% |
| Small Vessel Ischemic Disease | 2 | 1.2% |
| Unable to contact | 15 | 8.9% |
| Deceased at point of contact | 25 | 14.9% |
| Medication contraindication | 1 | .6% |
| Craniotomy | 1 | .6% |
| Epilepsy | 3 | 1.8% |
| Pacemaker | 1 | .6% |
| Substance Abuse | 1 | .6% |
| Unknown | 10 | 5.9% |
| Other | 9 | 5.4% |
| tDCS Concerns | 1 | .6% |
| **Total Screen Failures** | 167 | |
| **Total Screened** | 248 | |