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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

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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

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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%
Participants complete 1st assigned condition, cross over, and complete 2nd assigned condition	4-28	1.6%
Participants complete follow-up assessments 12 weeks after completion of the intervention	7-32	0%
Milestone Achieved: 1st participant consented, screened and enrolled	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 year. All regulatory documents including the study protocol and informed consent form were approved by the Penn IRB on July 28, 2020. Subsequent to IRB approval, we submitted HRPO documentation and after some back-and-forth received approval on 11/23/2020. Continuing Review approval for the 2021 year was obtained on 6/7/2021. Since submission of our semi-annual report, we continue to struggle with obtaining IRB approval from the Corporal Michael J. Crescenz Veterans Affairs Medical Center, 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. We continue to work with Penn's IRB and the VAMC to resolve this issue. Consequently, no study activity has taken place at the VAMC to date.

Study manuals have been created for all procedures beginning with recruitment/enrollment and spanning into data collection procedures for language assessments, therapy (CILT and tDCS) and MRI procedures.

The greatest challenge to our study progress has been the COVID-19 pandemic. Our lab spent much of the month of August 2020 putting measures in place to conduct research safely during COVID. We have made extensive use of PPE including masks, face shields/goggles, installed plexiglass barriers, and purchased air purifiers with HEPA filters. Unfortunately, the timing of HPRO document approval in November 2020 was during a severe period of the pandemic, prior to the introduction of COVID-19 vaccines, and was also during the holiday season, making it very difficult to recruit participants for in-person testing. During the COVID pandemic, we also experienced a setback in our staffing. Study staff for this projects had originally been hired and trained prior to the beginning of funding. However, in February 2021 we unexpectedly lost the research assistant assigned to this project. Unfortunately, due to hiring restrictions set forth by the University of Pennsylvania due to the COVID-19 pandemic, we were not able to replace this person until June 28, 2021. This has caused further delays to our ability to recruit subjects and we remain behind our enrollment goals.

We currently have 18 subjects that have expressed interest in participating, of those 5 passed the phone screening, 6 failed the phone screen and were deemed to not qualify, and 7 are awaiting to be contacted. We have enrolled 2 subjects. dPPA-01 has completed arm 1 of the study and begun arm 2 treatment the week of June 14th. dPPA-02 has completed arm 1 treatment and is currently in follow-up.

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?

Looking forward, our major goal for the next reporting period focuses on substantially increasing our recruitment and enrollment numbers. We were unable to start recruitment during the first 6 months for two main reasons: 1) the impact of the COVID-19 pandemic, both on subject availability and on the hiring of staff and 2) the iterative process of securing HRPO approval. We anticipate an acceleration of recruitment over the coming months as the COVID vaccine becomes more readily available and participant willingness to come into the lab increases. Additionally, we believe that our newly hired research assistant, who is a certified speech-language pathologist, will bring a higher level of expertise and productivity to subject outreach and data collection. We are also hiring a second full-time research assistant this August, who we anticipate will greatly accelerate study enrollment.

As of July 9, 2021, there are 7 patients who have been identified for further screening and possibly enrollment.

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:

On March 26, 2021, an IRB amendment was submitted for HRPO review and was determined to be “non-substantive”. On April 21, 2021 the changes were acknowledged and new study documents were added to the study file with no additional HRPO action needed. These changes are summarized below.

Changes in approach and reasons for change

After running our first participant, we realized that it is very unlikely that individuals who qualify for this trial will be able to complete the language testing in one visit. We have modified the ICF and protocol to add the caveat that the language assessments may vary from 1 to 3 visits depending on the participant’s stamina and dysfunction. We also find that it is unnecessary to have ALL tests repeated 2x at baseline – this is placing undue burden on the participant. We have modified the protocol so that only our main outcome measure (WAB and CILT) are repeated 2x at baseline. The other tests are spread out over the two visits.

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.

A second challenge to study progress, over the course of the past year, has been the COVID-19 pandemic. Our lab has dedicated considerable effort to putting measures in place to conduct research safely during the pandemic. Nonetheless, enrolling and running subjects has continued to be slower than planned in the winter/spring of 2021, largely due to participants apprehension. We anticipate an acceleration of recruitment over coming months as restrictions of the pandemic wind down (particularly as a greater proportion of patients, caregivers, and researchers undergo vaccination). In the meantime, we will continue to reach out to all persons who have been identified to us as potential subjects, so as not to lose access to these individuals who would have otherwise been recruited into the study during the pandemic.

A third challenge was employee turnover. The research assistant associated with this study left their position on February 5, 2021, and the hiring process to find a replacement was delayed due to University wide hiring freeze. However, we have been able to post the

position and as of June 28, 2021 hired a new RA. We are also in the process of hiring a second RA who we anticipate will start in August 2021.

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 Fasyeitan, No change.

Name:	*Leah Friedman*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	6 person months
Contribution to Project:	Trained on study procedures. Compiled study documents. Begun recruitment identification process.
Funding Support:	DoD CDMRP FY19 PRMRP (Award #: W81XWH-20-1-0490)

Name:	*Patrycja Puzio*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*N/A*
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

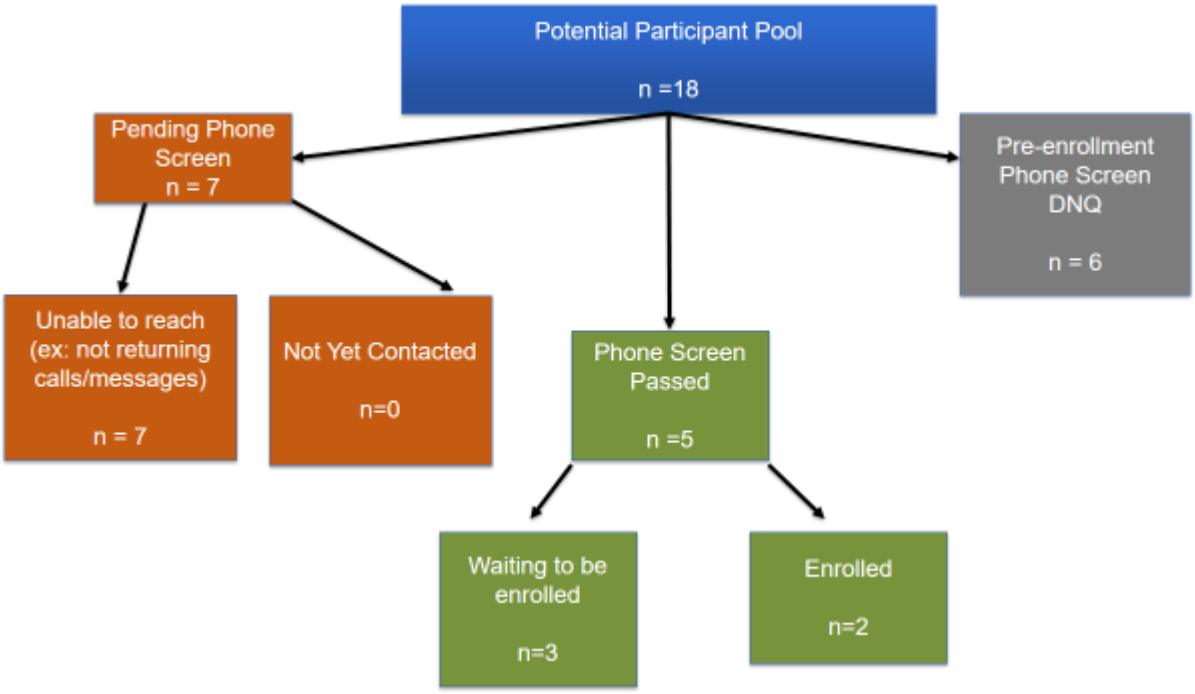

Table 1: Reason for Phone Screen Failures

Phone Screen Failures (n=6)		
Reason	**Number**	**Percentage**
Age out of range	**0**	**0%**
MMSE/ AD Diagnosis	**3**	**33.3%**
Non-native English speaker	**0**	**0%**
tDCS contraindication	**0**	**0%**
Not able to travel to treatment site	**3**	**33.3%**
Too much time commitment	**0**	**0%**
Concerned about brain stimulation	**0**	**0%**
Concerned about poor health	**0**	**0%**
Unable to contact/No longer interested	**0**	**0%**
Deceased at point of contact	**0**	**0%**