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Remotely Supervised (RS) tDCS for Primary Progressive Aphasia (PPA)

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NYULMC Study Number:	i22-01155
Regulatory Sponsor:	Leigh Charvet, PhD
Study Product:	tDCS 1x1 mini CT tDCS
Study Product Provider:	Soterix Medical Inc.
ClinicalTrials.gov Number	NCT05615922

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
COWAT	Controlled Oral Word Association Test
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IFG	Inferior Frontal Gyrus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
lvPPA	Logopenic Variant PPA
mA	Milliamperes
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
NSR	Non-significant risk
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
PPA	Primary Progressive Aphasia
QA	Quality Assurance
QAB	Quick Aphasia Battery
QC	Quality Control
RS-tDCS	Remotely-supervised transcranial direct current stimulation
SD	Standard Deviation
SAE	Serious Adverse Event/Serious Adverse Experience

SOP	Standard Operating Procedure
svPPA	Semantic Variant PPA
tDCS	Transcranial Direct Current Stimulation
US	United States
WAIS-IV	Wechsler Adult Intelligence Scale – 4th Edition

Protocol Summary

Title	Remotely Supervised Transcranial Direct Current Stimulation (tDCS) for Primary Progressive Aphasia (PPA)
Short Title	RS-tDCS for PPA
Brief Summary	Approximately 30 participants with PPA will be nationally-recruited in an open-label trial of a completely remote intervention to receive four weeks (5 x 30 min daily sessions per week) of active tDCS (2.0 mA, F7: left anodal) paired with simultaneous word naming practice
Objectives	- Evaluate the feasibility of RS-tDCS paired with word naming practice in patients with PPA - Collect preliminary efficacy data measured by change in scores on language assessment to support future grant applications
Methodology	Open Label Design
Endpoint	Primary Endpoints: - Feasibility judged by study completion percentage. The study will be deemed feasible if participants complete 16/20 RS-tDCS sessions Secondary Endpoints: - language assessment scores (QAB, BNT, COWAT) - The number of trained and untrained language probes identified at treatment end - Self-report questionnaires (ACOM, SAQOL-39, PROMIS Social Roles and Activities, and PROMIS Global Health)
Study Duration	2 years
Participant Duration	Approximately 1 month (4 weeks of intervention)
Duration of IP administration	20x30 minutes daily sessions of IFG tDCS combined with word naming practice
Population	N=30 participants (ages 45-85) diagnosed with early-stage primary progressive aphasia
Study Sites	NYU Langone Health 222 East 41st Street, 10th Floor New York, NY 10017
Number of participants	N=30 participants
Description of Study Procedure	tDCS is noninvasive brain stimulation device that modulate brain activity delivering a low-intensity electrical current (2.0 mA) through scalp sponge electrodes. The device is preprogrammed to ramp up to 2.0 mA (for 30 seconds), provide constant current throughout session (29 minutes), and then ramp down (for 30 seconds) at the end. Treatment is via telehealth visits, remotely and monitored through live videoconference using the established remotely supervised (RS) tDCS procedure. During the stimulation period, participants will engage in a picture naming exercise during the stimulation as guided by the study tDCS clinicians.
Key Procedures	Active tDCS with simultaneous word naming practice.

Statistical Analysis	To measure feasibility, individuals will be categorized as “compliant” based on the percentage of study visits completed (16/20). Compliance with the interventions will be assessed by summarizing the distributions of numbers and proportions of completed sessions. Preliminary efficacy will be measured by performance at baseline and study end across study measures (QAB, BNT, COWAT, self-report questionnaires). Change in scores, indicating change following intervention, will be calculated for each compliant participant (defined as above).

SCHEMATIC OF STUDY DESIGN

Prior to Enrollment	**Confirm eligibility criteria** via medical records and self-report; **Obtain informed consent**
Baseline Day 1	**Self-report questionnaires** (ACOM, SAQOL-39, PROMIS Social Roles and Activities, PROMIS Global Health) **Baseline Language Assessment** (Trained and Untrained Words, QAB, BNT, COWAT) **tDCS training and tolerability testing** **RS-tDCS + word naming practice**
Intervention Day 2 – Day 19	5 Days a week: **RS-tDCS + word naming practice**
Final Treatment Day Day 20	**RS-tDCS + word naming practice** **Post-intervention assessment** Post-stimulation language assessment (Trained and Untrained Words, QAB, BNT, COWAT) Self-report questionnaires (ACOM, SAQOL-39, PROMIS Social Roles and Activities, PROMIS Global Health)

1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

The goal of this open-label pilot study is to establish the feasibility of a program of remotely supervised transcranial direct current stimulation (RS-tDCS) paired with word naming practice for people living with the semantic or logopenic variants of primary progressive aphasia (PPA). We will also collect preliminary efficacy data for speech and language outcomes following treatment. These data will be used to inform a grant application to complete the next step of a randomized controlled trial.

Primary Progressive Aphasia (PPA) is a neurological condition associated with a gradual progressive decline in language function, affecting three in 100,000 people annually[1]**, which is a conservative estimate.** PPA is a devastating language-led neurodegenerative syndrome that is associated with atrophy of predominately left-hemisphere brain regions governing language. The three variants of PPA – semantic, logopenic, and nonfluent/agrammatic – are characterized by distinct neural areas of atrophy including frontal, temporal, and parietal regions[2,3]. The semantic variant is characterized by word knowledge loss; the logopenic variant by difficulties in word retrieval and repetition that are primarily phonologically mediated, and the nonfluent/agrammatic variant is differentiated by impairment in syntax and motor speech[4]. Beyond the devastating impact that PPA has on language, individuals living with PPA are often middle-aged when diagnosed, which negatively impacts family, work, and overall participation in social roles and activities[1].

Word naming is impaired across all three clinical variants of PPA[4]**.**
Word-finding difficulties are most pronounced in the early stages of PPA in the semantic and logopenic variants. However, word naming problems are not a salient feature of the nonfluent/agrammatic variant until an advanced stage of disease progression[5,6]. Targeting word naming training in PPA is of clinical relevance since difficulty finding words is among the chief early complaints[2]. Research suggests that word naming training in PPA can lead to improved language outcomes[7]. However, gains following language training alone remain relatively small[8]. Therefore, researchers have utilized neuromodulation as an adjunctive technique to improve word-naming outcomes.

One such neuromodulatory technique is tDCS, which is a type of noninvasive brain stimulation wherein a mild electrical current is passed through electrodes placed on the scalp. Delivering weak electrical currents (1.0-2.5 mA) via scalp electrodes, tDCS modulates neuronal excitation in the region where applied. tDCS has been extensively studied for a wide range of clinical applications and has a well-established record of safety and tolerability[9].

tDCS delivered while completing a trainingactivity can reinforce the learning that occurs to improve training outcomes. One established use of tDCS is to pair the stimulation with an ongoing or paired training activity to "boost" the training effect[10–12]. In this manner, the use of tDCS has been shown to lead to greater training outcomes from a range of training activities (motor, cognitive, speech and language) by increasing or decreasing the resting potential and/or firing rates[13]. Thus, repeated applications of stimulation facilitate neuroplasticity[14] through mechanisms of LTP of synapses[14–20].

tDCS must be dosed in a sustained and cumulative manner for adequate evaluation of its efficacy.
It is clear that tDCS effects are cumulative with adequate evaluation of behavioral effects requiring a period of multiple repeated applications[21]. Preclinical studies have demonstrated that stimulation results in sustained neuronal response[22], with increased sensitization following repeated application[21]. This effect is mirrored through consistent findings across clinical studies in that: **1)** a single tDCS session doesn't cause any meaningful behavioral response, and **2)** behavioral changes only follow a sustained period of daily treatment[23,24].

tDCS is a safe and tolerable treatment that can be delivered to participants at home using the remotely-supervised tDCS protocol[25]. We developed a remote protocol for use in clinical trials referred to as RS-tDCS, where each daily tDCS session is supervised live via videoconference in order to provide patients with access to the treatment remotely. We have extensive experience in delivering remote tDCS treatment to people living with multiple sclerosis (MS) and an extensive range of other neurological and psychiatric conditions. We also have a clinical tDCS virtual health program where we provide remote tDCS to patients with many different conditions[26,27].

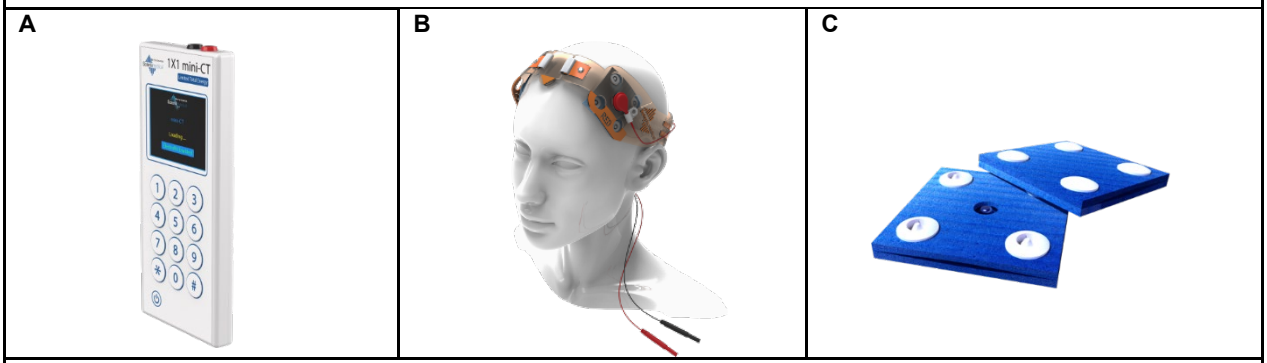
When targeted to the inferior frontal gyrus (IFG), tDCS has been shown to improve word naming among individuals with word finding difficulties. The IFG is a key neural circuit for word naming[28–30]. tDCS has been used in people with aphasia when it is paired with language training. Through both research[26,31] and our clinical service[27], we have initial experience providing RS-tDCS paired with language activities to people living with aphasia. Among individuals with PPA, a recent meta-analysis strongly suggests that language training alongside tDCS exceeds the gains made through language training alone[32], with the left IFG as a common neural target across naming studies. Furthermore, we have led the field in determining the feasibility of remotely-supervised tDCS (RS-tDCS) for individuals with PPA with differing typologies and various degrees of severity[31]. However, no study to date has systematically investigated the feasibility and acceptability of RS-tDCS paired with language training in PPA.

In the context of this progressive condition, the treatment goal is to extend the preservation of language functioning through the use of tDCS paired with word naming practice. In this open-label pilot study, we will measure the use of RS-tDCS in people with PPA. It is important for us to first demonstrate the acceptability and feasibility of the treatment. We will also pilot secondary clinical efficacy outcomes, to target personally relevant known words rather than attempting to restore access to forgotten words[33,34]. Research suggests that recall is higher among those with PPA who have trained words of functional relevance compared to an untrained set of words[33,35,36]. This study uniquely pairs the evidence from behaviorally-based language training studies in PPA alongside our established RS-tDCS protocol, allowing for determination of the clinical efficacy of tDCS as an adjuvant to PPA treatment.

2.2 Name and Description of the Investigational Device

- **1x1 Mini-CT tDCS device** *(Soterix Medical Inc.)*: The 1x1 Mini-CT tDCS device (see Fig.1, *Panel A*), through the accompanying headset (Fig. 1, *Panel B*) and sponge electrodes (Fig.1, *Panel C*), delivers a weak electrical current (1.0-2.0 mA) to target a specific area of the brain. It is a powered device (9 V) and is easily operated, with a user-friendly large-button keypad interface. The device has specific functions and features that guarantee safety in the remote supervised administration and uniform stimulation dose across sessions and participants. The device allows strict dose control and usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session.

Figure 1. Equipment for tDCS intervention



Panel A: 1x1 Mini-CT tDCS device; *Panel B:* SNAPstrap Headgear; *Panel C:* EASYpad Electrodes

2.2.1 Preclinical Data

N/A

2.2.2 Clinical Data to Date

Feasibility of RS-tDCS. We have led the field in remote brain stimulation with the development of the RS-tDCS platform[37–47]. In our protocol, participants are provided with remotely-controlled tDCS device, trained in safe and effective operation, and then supervised for daily use through live videoconference[48] (VSee[48]). Our updated videoconference software for this study will be Zoom. The telehealth connection has resulted in high retention rates across repeated and extended sessions (e.g., >97% completion rates across RCTs to date[37–47]). Extensively tested over > 7 years (>9000 remote tDCS sessions in >400 patients to date), it is well validated for use in MS and generalizable for use across most other clinical populations[37–47] (ages 18-85 years, range of neurological and psychiatric conditions, including those with advanced disabilities and/or limited technical experience, and reaching those at socioeconomic disadvantage). Further, the RS-tDCS platform has allowed for continued enrollment of patients with MS in ongoing RCTs during the COVID-19 onsite clinical research pause[49–52] (with >100 participants by completing all study procedures remotely).

IFG tDCS regulates language difficulties. IFG tDCS has been established to regulate language difficulties (e.g., in PPA and post-stroke aphasia). In subanalyses of nondepressed MS participants with high baseline negative affect[53], 10 or more RS-tDCS sessions, led to reliable negative affect reduction, and the negative affect reduction was maintained at 1-month follow-up. Importantly, these changes have also been linked to increased functional connectivity in Broca's area following treatment[54].

2.2.3 Dose Rationale

The tDCS protocol of this proposed research will use a stimulation intensity of 2.0 mA that falls well within safety limits established by numerous previous studies applying tDCS with human subjects.

2.3 Rationale

The application of tDCS for language difficulty is not novel on its own[32]. However, all studies of tDCS in PPA have required onsite delivery of treatment, resulting in small sample sizes and few sessions administered (likely underdosing)[2,55,56]. Therefore, our main objective is to evaluate the feasibility of reaching PPA participants for study remotely. We will evaluate preliminary efficacy by measuring language output before and after the treatment period.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Risks of tDCS: The repeated application of tDCS as proposed in this study poses a non-significant risk (NSR) to participants. The safety of this technique has been addressed and tested by multiple researchers who have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only mild and transient side effects with no report of serious adverse event related to tDCS across clinical trials to date. In >9,000 participant, no undesirable or long-lasting effects have been reported, nor have any subjects reportedly abandoned a study due to discomfort. The most common side effects are warming sensation, itching or tingling sensation under the area of the electrodes. The tDCS protocol of this proposed research will use a stimulation intensity of 2.0 mA that falls well within safety limits established by numerous previous studies applying tDCS with human subjects. In both active and sham tDCS treatment arms, there could be mild discomfort from wearing the headgear.

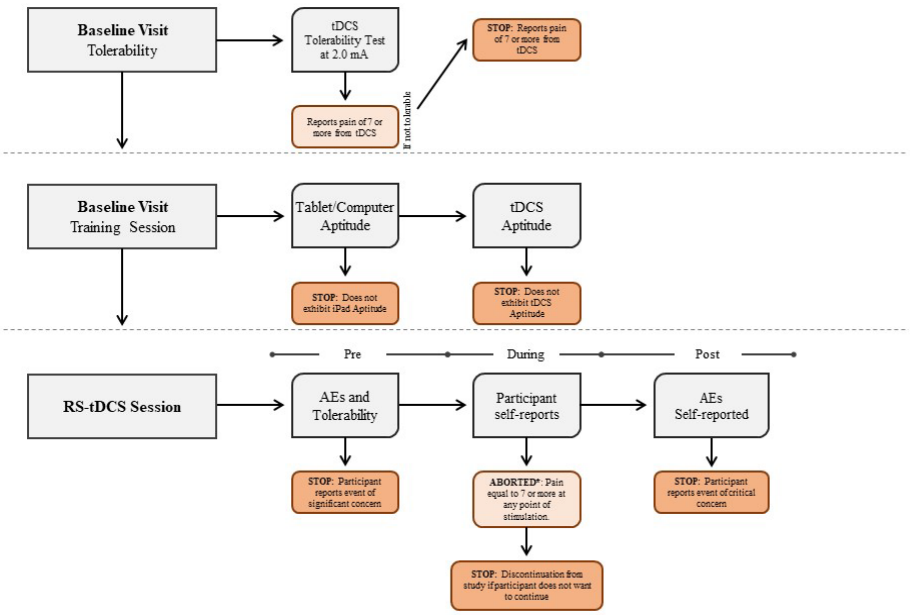
The protocol is designed to have a decision-tree series of checkpoints with "STOP" criteria that must be cleared in order to proceed at each step (see Fig.2).

Risks of RS-tDCS: Extensively verified safety and tolerability of RS-tDCS in the context of research[26] and specifically in people with aphasia[31] based on this experience and well-established safety/tolerability of tDCS in general, we do not anticipate adverse events to be frequent or treatment limiting. No serious adverse events occurred following 6,779 sessions of RS-tDCS[26]. However, adverse event reporting will occur at each session and risk will be systemically monitored and minimized as outlined in Section 9.7.1. Dr. Krupp will serve as medical monitor for this study as she has served for all NYU Langone MS Comprehensive Care Center tDCS studies to date. Quarterly meetings will be help with Dr. Krupp to review adverse events and any adverse event that is judged to be treatment limiting or severe will be immediately addressed by Dr. Krupp per standard medical care and reported to IRB following guidelines. If a serious adverse event occurs, stimulation will be stopped, participants will be instructed to remove the headset, and to either dial 911 or contact their treating neurologist for follow-up. A

member of the study team will follow up with subjects within the next 1-7 days after such events to document the resolution. This process will be same for both NYU and non-NYU patients. If these cases do occur, treatment will not resume until Dr. Krupp gives medical clearance to proceed.

Participants will be visually surveyed to rate discomfort on a Likert scale from 1-10 at 3 time points during treatment (session 1, midway, and session 20). If a participant reports a score of 7 or higher for discomfort, the session will be stopped and the study member will consult with the participant for any adjustments needed. Session will start one time again with participant agreement, but will be terminated if a second discomfort score of 7 or higher is reported. Sessions will also be ended if at any point in time if a participant spontaneously reports a discomfort score of 7 or higher. Based on extensive experience[26], we have established that this type of discomfort rating will capture any potential type of adverse events as they may occur.

Figure 2. Session safety and tolerability checkpoints and stop criteria



* the supervising study technician intervenes to assess the subject's safety and abort the session when necessary.

Word naming practice: Word naming practice is not associated with any known risk. To minimize possible frustrating feeling, each session will be monitored in real-time via HIPAA-compliant videoconference with a trained study technician.

Self-report questionnaires: Completing questionnaires about one's language use may produce some discomfort and/or emotional distress in some patients. Participants will be allowed to take breaks as needed and may skip questions they do not feel comfortable answering so long as the questions do not affect analysis of primary endpoints or eligibility criteria. Individuals with diagnosed psychiatric disorders will be identified by their physician prior to enrollment and would therefore not meet inclusion criteria. While we don't anticipate this population to have suicidal ideation, the study will follow standard clinical procedures if a subject is suicidal (e.g. refer subject to closest emergency room).

2.4.1.1 Other Risks

Breach of Confidentiality: There is minimal risk of breach of confidentiality. Participants will be assigned a unique study ID and their name will not be used on any of the data collected. All study data survey will be acquired through REDCap and the printed records will be stored in lock cabinet at 222 E 41st Street, 10th Floor. Any study data stored

on secure NYU computers and servers will be de-identified. The results of these data collected may be used for publication but will not include the participants' names.

Unforeseeable Risks: While not expected, there may be risks associated with tDCS that are not known at this time.

2.4.2 Known Potential Benefits

Some participants may receive benefit from the word naming practice. There is robust research on the benefits of such interventions among individuals with aphasia.

Based on the literature to date, we anticipate that tDCS combined with word naming practice may improve language functioning among individuals with PPA[56,57].

This will be one of the first studies to evaluate a tele-intervention program of tDCS for speech and word naming practice among patients with PPA. The project has the potential to produce an immediately available treatment option for language difficulties among individuals with PPA. This would have immediate and significant clinical utility. In particular, the benefit to the field is the availability of a treatment option for managing symptom burden associated with PPA.

3 Objectives and Purpose

3.1 Primary Objective

To evaluate the feasibility of an RS-tDCS service and concurrent word naming practice.

3.2 Secondary Objectives

Secondary objectives include exploratory analyses to evaluate the potential benefits of tDCS + word naming practice through change scores on language outcomes. This data will inform the power analysis for future study development.

4 Study Design and Endpoints

4.1 Description of Study Design

This study will recruit n=30 PPA patients to receive 20x30 min sessions of active 2.0mA tDCS, combined with simultaneous word naming practice over a 4-week period.

All participants will have a remote consent/research screening visit, baseline visit, 20 tDCS treatment visits, and post-treatment assessment. All visits will be completed remotely using Zoom.

This will be a single site study at NYU Langone Health and will take place over a 2-year period.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

- Feasibility judged by study completion percentage (16/20 sessions completed per participant)

4.2.2 Exploratory Clinical Endpoints

- Change in language assessment scores (QAB, BNT, COWAT) and self-report questionnaires (ACOM, SAQOL-39, PROMIS Social Roles and Activities, PROMIS Global Health) will be assessed.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ages 45-85 (inclusive)
2. Primary progressive aphasia diagnosis (logopenic or semantic variant)
3. Wide Range Achievement Test (WRAT) score < -1.5 SD, serving as a literacy proxy for premorbid cognitive ability and ensuring English language fluency sufficient for participation in the study procedures. If participants are not fluent enough to perform this task, the Peabody Picture Vocabulary Test (PPVT) will instead be administered with the same cut-off score of < -1.5 SD.
4. WAIS-IV Matrix Reasoning T score < 20, serving as an index of current general cognitive functioning to exclude those with severe cognitive impairment
5. Stable and continuous access to internet service, email (WiFi "hotspot" to be provided if needed)
6. Fluent in English language (due to outcomes validated in English versions only)

Inclusion criteria may be confirmed through medical records, screening assessments and self-report.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Disorder other than PPA known to cause language dysfunction
2. Diagnosis of nonfluent/agrammatic subtype of primary progressive aphasia
3. History of traumatic brain injury
4. Uncontrolled seizure disorder and/or recent (<5 years) history of seizure
5. Metal implants in the head or neck
6. Any skin disorder or skin sensitive area near stimulation locations
7. Pregnant or breastfeeding. Given the age range of our potential participants, we do not anticipate excluding anyone on the basis of pregnancy or breastfeeding. While there are no known or theoretical safety risks of tDCS in this special population, we routinely have included this eligibility in all our tDCS studies to date out of an abundance of caution. Further, in reference to our outcomes for this study, pregnancy and/or breastfeeding status may have unique cognitive features secondary to the influence of hormones. Participants should not become pregnant while participating in this study. If they are able to become pregnant, they will be required to use a medically-accepted method of birth control while they participate in the study:
    - Hormonal methods like birth control pills, patches, vaginal rings or implants
    - Barrier methods such as condoms or a diaphragm used with spermicide (a foam, cream or gel that kills sperm)
    - Intrauterine device (IUD)
    - Abstinence (no sex)

*Exclusion criteria may be confirmed through medical records, screening assessments and self-report***.**

5.3 Vulnerable Subjects

We will enroll PPA patients early in the disease course and with language loss as their primary impairment. To ensure the ability to meaningfully participate, consistent with all of our RS-tDCS protocols, we will screen to include participants with premorbid intellectual functioning in at least the average range, and screen to exclude those participants with severely impaired current level of cognitive functioning. Consistent with our RS-tDCS protocol, premorbid cognitive impairment will be estimated using the verbal Wide Range Achievement Test-4th edition (WRAT-IV) or the nonverbal Peabody Picture Vocabulary Test-4th edition (PPVT-4) as a proxy of expressive vocabulary, which is an established method to estimate premorbid cognitive ability. A cut off of 1.5 SD below age normative means will be used for exclusion criteria. Current level of cognitive functioning cognitive functioning will be estimated using the nonverbal Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV) that measures abstract reasoning. A cut-off of 3 SD below age normative means (indicating greater than moderate impairment) will be used for exclusion criteria.

5.4 Strategies for Recruitment and Retention

Potential subjects who meet the eligibility requirements as determined by the inclusion and exclusion criteria will be contacted by a trained member of the study team. Diagnosis of PPA and tDCS eligibility will be confirmed by medical record review and a signed tDCS safety form sent to study staff prior to study enrollment.

A patient who is seeing one of these medical staff members as their treating clinician will be introduced to the study by that medical staff member. If the patient is interested and agrees to be contacted, a team member will contact them on the phone (or in-person if participant is already in clinic) using an IRB-approved phone script to provide additional study information and pre-screen to assess eligibility. Verbal responses will be recorded on a separate pre-screen verbal checklist. For any subject who is ineligible, or who is eligible but decides not to participate, we will immediately destroy the data collected during the pre-screen.

An IRB approved flyer will be posted in local physician offices and waiting rooms and throughout NYU and support organizations. In addition to recruitment at NYU, we will post these flyers around the Ambulatory Care Center (ACC) for patients to recruit from the entirety of the Neurology department and from any number of people who come to visit the ACC on E38th Street or have an appointment at E41st Street.

An IRB approved study description will be posted on PPA related websites and shared with appropriate list-services related to those websites.

Diagnosis of PPA will be confirmed by patient medical records. Non-NYU patients will be asked to submit their medical records for confirmation. All patients will complete a tDCS safety questionnaire to confirm eligibility for tDCS administration (e.g. no metal in head or neck, history of epilepsy, etc.)

A description of the study including objectives and the expectations of the subject's participation will be explained. Potential participants will be clearly informed that they have the right not to participate in the study and that declining participation will not in any way affect their clinical care at NYU Langone Health. Subjects will additionally verbally confirm if they meet eligibility criteria.

Consent and assent of study participants will take place in a private telecommunication room (Zoom).

Recruitment procedures will be conducted in private patient rooms during direct subject encounters with their healthcare provider. Any identifiable data that is collected during recruitment will be kept in a locked filing cabinet in a locked office. Any identifiable data from screening failures will be destroyed immediately after the recruitment period has ended. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.1 Informed Consent Process

Consent forms describing in detail the study device, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention / administering study product. The following consent materials are submitted with this protocol: informed consent form.

5.1.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their relatives or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Subjects may be mailed an informed consent form and a link to the Zoom room to meet in after they have reviewed the consent. The study team member will then explain the consent to the subject, and ask if the subject has any

questions. If the subject agrees to participate, they will sign the informed consent document and mail it back to the study team via a provided return label. Alternatively, the consent form may be sent via email by a study team member for the participant to print, sign, and return via SendSafe. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

Capacity to Consent
Subject capacity to provide informed consent will be determined by trained team members or PI who will ask the participant open-ended questions regarding their understanding of key research information. All team members will be trained in GCP-ICH guidelines and will receive additional training by the PI or an experienced study team member. Global cognition will be assessed using resources accommodated for individuals with language impairment (WRAT-IV or PPVT-4, WAIS-IV Matrix Reasoning). These measures will be given prior to study enrollment with scores greater than 3.0 SD's below age-normative scores being a cut-off for study inclusion.

The results of the capacity assessment (WRAT-IV or PPVT-4, and WAIS-IV Matrix Reasoning) will not be placed in the subject's medical record. This information will only be used for research purposes and will not be considered clinical data.

Prospective subjects will be informed of the results of the capacity assessment after it's conducted. If an individual is found not to have the capacity to consent, the assessor will explain this to the individual. The assessor will provide the necessary resources and referrals for further care and evaluation.

Ongoing Assessment of Capacity
At each study visit, subjects will have direct interaction with the licensed clinicians referenced above. If the licensed clinicians have any concerns about the subject's capacity, a formal capacity assessment will be conducted as described above.

Over the course of the study, it is possible that a subject who had capacity at enrollment may lose capacity or capacity may fluctuate. Subjects who lose capacity will be withdrawn. Subjects who appear to be unduly distressed will be withdrawn from the research in a manner consistent with good clinical practice.

5.2 Duration of Study Participation
Study participation will last approximately 1 month and will include:

- Remote consent (20 minutes), with participant provided as much time as they need to review consent form. Once consented, participant will be scheduled for telehealth research screening. The screening will be scheduled based on participant and study/physician availability, which can occur on the same day as consent and anticipated to be within one week of consent.
- Baseline speech and language assessment & tDCS Session 1 (approximately 3 hours: 20 minutes to orient to device, 1.5 hour assessments, 30 minute tDCS session, 15 additional minutes of word naming practice).
- tDCS treatment sessions (20 x 30 min session over 4 weeks)
- tDCS Session 20 & Treatment-end (2 hours)

5.3 Total Number of Participants and Sites
Recruitment will end when approximately 30 participants are enrolled (sign consent) through NYU Langone Health, Department of Neurology.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination
Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Participant Withdrawals or Termination

If a participant wishes to withdraw from the study they may do so at any point without adverse effect on their standard-of-care treatment. Participants will be provided with study team e-mail and contact number and can withdraw at any time.

5.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Device Intervention

6.1 Study Device Description

tDCS is a device that delivers weak electrical current (2.0 mA) through sponge electrodes placed on the scalp. The main components are:

- **1x1 Mini CT tDCS device:** The device is powered by 9-volt (V) rechargeable batteries. The device can be easily operated, with a user-friendly large-button keypad interface. The device allows strict dose control and usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session. The high sensitivity of the device to any changes allows us to monitor in real time the contact quality between the surface of the electrode and the skin ensuring safety and high quality of the delivered stimulation.
    - **tDCS Headset:** The headset will be used to standardize and simplify the electrode placement. The headset uses two electrodes: the anode electrode and the cathode electrode. An electrode montage targeting the left frontotemporal lobe (anode over F7 and cathode over O1) electrode montage will be used. The headset connects to the tDCS device with two wires (anode and cathode).
- **Sponge electrodes:** The electrodes are square (5 x 5 cm^2) pre-saturated saline sponge electrodes packaged for single use equipped with snaps to fasten the sponges to the headset. The participant will be only required to open the package and snap the sponge onto the headset. The use of pre-moistened, single-use electrodes avoids the possibility of over-saturating the sponge as this can saturate the hair, affecting the spread and the direction of the current flow.

tDCS is a non-significant risk device because it is:

1. not intended as an implant.
2. it is not purported or represented to be for use supporting or sustaining human life.
3. it is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise prevent impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject. tDCS has an established record of safety and tolerability for use from trials in a range of neurological and psychiatric condtions[58] [59], and including the specific remotely supervised and remote use as proposed for this study[60] [61]. It has NSR designation for our trials specifically using the proposed procedures in participants with MS[62] [63] [64] [65] [66] [67] [68] as well as for use as an NYU Langone Health approval as innovative care for our tDCS clinical service program[69].
4. it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject

6.1.1 Acquisition
The devices used in the NYU Langone RS-tDCS research program are manufactured by Soterix Medical Inc. and owned by NYULH.

6.1.2 Product Storage and Stability
Devices, when not allocated to participants, are stored in-house in a locked room. Device allocation notes including device serial number and device unlock codes will be stored for reference.

6.1.3 Device Programming
To ensure blinding, devices will be pre-programmed in advance by an independent staff member, who will not take part in the treatment and assessment[70–72]. The device is programmed to ramp up to 2.0 mA (for 30 seconds), provide constant current throughout session (29 minutes), and then ramp down (for 30 seconds) at the end.

6.1.4 Dosing and Administration
The tDCS device will deliver each session 2.0 mA for 30 minutes over the left frontotemporal lobe with focus on the inferior frontal gyrus (IFG). Participants will receive 20 intervention sessions over the course of this study on weekdays (M-F).

Study technicians are always live with participants via Zoom when initiating and delivering the treatment and can address any issues that arise during treatment. Study technicians will direct headset placement remotely. The tDCS device can only operate if: **1)** the headset is correctly placed for adequate connection, and **2)** the study technician provides a session code that unlocks the device for a one-time only 30-minute period of use.

If the device loses adequate electrode contact for any reason, the device will automatically discontinue the session. The session can only be reestablished if another unlock code is provided by the study technician.
Specific stop criteria are outlined for treatment administration. Should any stop criteria be met at any point in administration of treatment, the participant will not undergo any further treatments and will be asked to return the study equipment. If the participant wishes to discontinue a session, they may press the "abort" key at any time, which ramps down and stops the stimulation current within 30 seconds.

6.1.5 Route of Administration
tDCS is administered through a paired of sponge electrodes placed on the scalp using the headset. The device allows strict usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session.

6.1.6 Duration of Intervention
Participants will complete 20 sessions of active RS-tDCS over the course of approximately 4 weeks. The tDCS will be programmed to deliver 30 minutes of stimulation.

6.1.7 Device Specific Considerations
- Device size: Height 7.2 in; Width 3.6 in; Depth 1.2 in
- Device model: Model 1601
- Device settings and programming: Double-blind option: Sham (ON/OFF), Secure administrator mode to program sessions, storage of data and codes of 250 sessions; SMARTscan to provide continuous visual indication of electrode quality during stimulation

6.2 Study Device Accountability Procedures
The device accountability and inventory log will be used to log device-use including subject ID, date shipped, dates used, session technician, and date returned.

7 Study Behavioral Intervention
7.1.1 Word Naming Practice
Each tDCS session will include simultaneous word naming practice via live video visit supervision with the trained tDCS clinician. tDCS clinicians for this study will be experienced psychometricians with master's level training and

supervised by speech and language pathologist, Dr. Vogel-Eyny. Consistent with the protocol outlined by Flurie et al, 2020, study participants, with caregiver support, will select 100 treatment items of personal relevance (i.e., high familiarity and frequency) from a fixed list of 220 possible items representing everyday objects (nouns) and actions (verbs) (e.g., hat, toothbrush, book, supermarket, coffee, cooking, reading)[33]. Unselected items from the original list of 220 items served as the control word naming list. Baseline performance will dictate the number of words reviewed per treatment session to reduce the burden on participants.

During each RS-tDCS session, once the stimulation has been activated the tDCS clinician will guide the participant in the word naming practice. Following the procedures of Henry et al. (2019), participants will be presented with photos of target items (via Zoom) and prompted to verbally produce the names of the pictures (common nouns and verbs) with the support of a word naming cueing hierarchy aimed at facilitating word retrieval through self-cueing[35]. Participants will be guided as needed through the prompting of semantic, orthographic, and phonological information about the target word. All cues within the hierarchy will be presented to the participant for each item whether they correctly identify the stimulus or not. This is in effort to reinforce lexical retrieval of the target stimuli. The word naming approach is consistent across all participants in the study and described in detail below and outlined in Table 1.

- Semantic Self-Cue
  - When a target picture is presented for naming, the participant will first be instructed to generate semantic features/conceptual information using a fixed set of questions (e.g., “Where do you find it?” “What is it used for?”). At this stage, participants are also asked to provide any personal historical information about the target (e.g., “I drink this every morning”).

- Orthographic Self-Cue
  - Next, participants are asked about any orthographic (written) information they might have about the word (i.e., whether they can write the word or the first letter of the word).

- Phonemic Self-Cue
  - Participants are then asked to provide phonological or sound-based information about the word (e.g., the initial sound). If the participant cannot retrieve any aspect of the orthographic (written) or phonological (sound form) of the target, they are given the first letter of the target (e.g., for “coffee” they would be given the letter “c”) and will be asked to produce the corresponding sound of the letter. If the participant cannot produce the corresponding sound then the technician will provide it.

- Oral Reading
  - Should the participant still be unable to name the word, the written form will be provided for oral reading. If the participant has difficulty reading the target word, then the spoken form will be given.

- Written and Spoken Repetition
  - After these steps, the spoken and written forms for the target is named three times.

- Yes/No Questions
  - Then yes/no questions are given to the participant (e.g., “Do you use this in your hair?”).

- Recall
  - Finally, participants are asked to provide two semantic characteristics about the target (e.g., for coffee, participant might say, “you drink it”) and attempt to name and write the word.
  - Regardless of whether the participant is able to name the target at any step, they continued with the remaining steps (excluding the yes/no questions).

Table 1. Word Naming Practice Cues

Training Step	Procedure	Instructions

1. Semantic self-cue	Picture presented; patient prompted for semantic information and/or autobiographical information	What can you tell me about it? (Where do you find it? What is it used for? What is it made of?)
2. Orthographic self-cue	Prompt written form or first letter of word	Can you write the word? Can you write the first letter?
3. Phonemic self-cue	Prompt initial phoneme	What sound does that letter make? What is the first sound of the word?
4. Oral reading	If item not named, provide written form and participant reads aloud	Here is the word. Can you read it?
5. Written and spoken repetition	Participant writes and says the word three times	Now write and say the word (three times).
6. Yes/no question	Provide participants with yes/no questions.	E.g., Is it sweet? Can you buy it at the supermarket?
8. Recall	Participant provides two semantic features and writes and says the word.	Now tell me two important things about this item. What is this called? Can you write it?

Adapted from Henry et al., 2019.

7.1.2 Administration of Intervention

Participants may receive a laptop computer with access to Zoom if they do not already have the necessary resources to virtually meet with a study technician. All study procedures requiring contact with a study clinician (RS-tDCS, language assessment, and word naming practice) will be conducted using this laptop and Zoom connection.

8 Study Procedures and Schedule

8.1 Study Procedures

- Pre-screening:
  - Diagnosis of PPA and tDCS eligibility will be confirmed via medical records.

After subjects provide written informed consent, the following research procedures will take place over approximately 2 weeks:

- Baseline Visit:
  - Following procedures for our validated protocol[37–41,43–47], participants will first receive training on the use of the tDCS device and headset.
  - Participants will undergo a 90-second tDCS tolerability test to ensure the stimulation is tolerable. The participant will be given a one-time use code to initiate the stimulation, the tDCS device will

ramp up to its target stimulation intensity (2.0mA) and after 90 seconds, participants will be instructed to press "0" to stop the test. Participants are free to stop the test at any time before the 90 seconds. Participants will then be instructed to remove the headset. Participants who cannot tolerate 2.0 mA will be considered a screen failure.

- Participants will complete self-report questionnaires about their language use and daily functioning through REDCap survey function (see assessments section 8.2 below).
- Participants will identify a list of high frequency common nouns and verbs that they use in their daily life. This list of words will then be utilized to make the trained and untrained stimuli lists.
- For exploratory research, participants will complete cognitive measures (QAB, BNT, COWAT).

- tDCS Session 1:
  - Participants will have their first 30-minute remote session of 2.0mA active tDCS combined with word naming practice. Participants will be presented with the list of common nouns and verbs previously identified and practice verbally identifying those words from pictures with the help of a lexica retrieval cuing hierarchy. At each treatment session, participants will complete brief adverse event reports before and after each session. Once the study technician visually confirms correct headset placement and participants confirms adequate contact quality (moderate or good), the technician will provide the participant with a one-time use unlock code to enter into their tDCS device. The participant enters the code when ready to initiate the stimulation. During each stimulation session participants will listen to a guided mindfulness meditation audio track on the study provided laptop computer.

- Remotely-Supervised tDCS Sessions 2-20:
  - Over the next 4 weeks, participants will complete the remaining daily RS-tDCS + word naming practice as described above for session 1.
  - tDCS session 20 & Treatment-end: After completing the final tDCS session, participants will repeat the baseline self-report questionnaires and language assessment. Participants will be asked to return the equipment via Fedex using a prepaid return label.

8.2 Study Assessments

8.2.1 Self-Report Questionnaires

- The Aphasia Communication Outcome Measure (ACOM): A measurement of patient-reported communicative functioning in aphasia[73].
- Stroke and Aphasia Quality of Life-39 Item (SAQOL-39): A measurement of quality of life among individuals with aphasia[74].
- Patient-Reported Outcomes Measurement Information System (PROMIS) – Social Roles and Activities: A measurement of the perceived ability to perform one's usual social roles and activities[75].
- Patient-Reported Outcomes Measurement Information System (PROMIS) - Global Health: A measurement of symptoms, functioning, and healthcare-related quality of life[75].

8.2.2 Cognitive and PPA symptoms Assessments (Exploratory)

- Trained and Untrained Words: Participants will verbally name pictures of common nouns and verbs with the support of a lexical retrieval cueing hierarchy aimed at facilitating word retrieval through self-cueing[35].
- Quick Aphasia Battery- (QAB): This aim of the QAB is to provide a reliable and multidimensional assessment of language function in a shorter time period across 8 language subtests [76]. QAB has been adapted for remote use.
- Boston Naming Test (BNT)-Short form: Consists of 15 line-drawn pictures presented in order of difficulty from "easiest" (e.g., "house") to "most difficult" (e.g., "palette"). Participants have 20 seconds to name each item correctly with a cueing hierarchy[77].

- Controlled Oral Word Association Test (COWAT): A measure of verbal (phonemic and semantic) fluency where participants are given 60 seconds to name all of the words within a given category[78].

8.3 Study Schedule

8.3.1 Pre-Screening

- Conduct eligibility phone screen to assess general eligibility.
- PPA diagnosis and tDCS eligibility determined via medical records and tDCS safety questionnaire
- Eligible participants will be scheduled for a baseline visit.

8.3.2 Consent & Telehealth medical screening

- Remote consent through SendSafe (*20 minutes*)
  Once consented, study personnel will send tDCS and study materials to participant

8.3.3 Baseline Visit (visit 1)

- Baseline language assessment (*1.5 hours)*
- Self-report questionnaires (*20 minutes)*

8.3.4 tDCS Session 1 (Visit 2)

- Train participant to use tDCS device (20 *minutes*)
- Perform tDCS tolerability test (*2 minutes*)
- Complete first remotely-supervised tDCS session + language skills practice *(45 minutes)*

8.3.5 Remotely-Supervised tDCS sessions 2-19 (Visits 3-20)

- 20x30 minutes of active tDCS with simultaneous language skills practice (*45 minutes*)
- AE reporting

8.3.6 tDCS Session 20 & Treatment-end Visit (Visit 21)

- Participants will complete tDCS and word naming practice session 20 (*45 minutes)*
- Post-stimulation language assessment *(1.5 hours)*
  Equipment return

9 Assessment of Safety

9.1 Definition of Adverse Events (AE)

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

9.1.1 Definition of Serious Adverse Events (SAE)

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

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

9.1.2 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.1.3 Reporting of Pregnancy
Women who are pregnant or breastfeeding as determined by participant self-report or medical record will not be included in this study. Women who cannot confirm their pregnancy status via self-report or medical record will be excluded.

9.2 Classification of an Adverse Event

9.2.1 Severity of Event
For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

9.2.2 Relationship to Study Agent
The clinician's assessment of an AE's relationship to study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*

- ***Possibly Related*** *– The AE may be related to the device. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

9.2.3 Expectedness

Dr. Charvet will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.4 Reporting Procedures – Notifying the IRB

9.4.1 Adverse Event Reporting

Adverse event rates will be calculated and reviewed at DSMP meetings. Adverse event rates will be reported to the IRB as described previously. Should adverse event rates exceed the normal rates observed in the literature, the study PI will place the study on hold and review the safety of the study.

9.4.2 Serious Adverse Event Reporting

Serious adverse events that are related to the study device or interventions will be reported to the IRB within 24 hours of becoming aware of the occurrence.

9.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 5 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 10 business days of the IR's receipt of the report of the problem from the investigator.

9.5 *Reporting Procedures – Notifying the Study Sponsor*

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

9.6 Study Halting Rules

There are no predetermined stopping rules.

9.7 Safety Oversight

9.7.1 Data Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the data safety monitoring of the study at his/her site. Data safety monitoring meetings will occur with every 10th subject enrolled (beginning when first participant is enrolled) and will include careful assessment of research procedures including protocol adherence, regulatory documentation, enrollment (e.g. rate of enrollment, screen fails, withdrawals), unanticipated problems (e.g. device malfunction, connection issues), and any issues that may arise during the course of research. There are no predefined stopping rules.

Meetings will be documented in data safety monitoring reports (DSMR). An annual DSMR will be submitted to the IRB at the time of continuing review. This data safety monitoring will include careful assessment (e.g. frequency, relatedness, and expectancy) and appropriate reporting of adverse events (e.g. skin tingling, itching, warming, irritation) as noted above. Each tDCS administration will occur in the context of a live video visit through Zoom. With this real-time supervision of treatment, risk will be systematically monitored and minimized.

9.7.2 Medical Monitoring

Dr. Lauren Krupp, MD, Director of the NYU Langone MSCCC, will serve as medical monitor for this study and will be involved in data safety monitoring. Consistent with her ongoing role for the NYU Langone Health tDCS Program, Dr. Krupp will be responsible for resolving any clinical matters that may arise (e.g., unanticipated side effects of tDCS), including careful assessment of the number and type of serious adverse events, determining relatedness to the research, and resolution. This will be done through quarterly meetings with Dr. Krupp to review adverse events. Any adverse event that is judged to be treatment limiting or severe will be immediately addressed by Dr. Krupp per standard medical care and reported to IRB following guidelines. If these cases do occur, treatment will not resume until Dr. Krupp gives medical clearance to proceed.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

Study data will be collected through REDCap survey function, and these records will be printed and stored in a locked cabinet only accessible to the research staff. While survey data is collected via REDCap, no data will be stored in REDCap. All data will be destroyed from REDCap after it is transferred for storage.

10.2 Statistical Hypotheses

This is a pilot test to assess the feasibility of RS-tDCS with word naming practice. The primary outcome measure will be percent compliance (e.g., at least 16/20 RS-tDCS sessions completed per participant).

In exploratory analyses, pre- and post- language assessment outcomes (trained and untrained words, QAB, BNT, COWAT) will be compared to determine if the intervention led to improved scores. Descriptive analyses will be completed to identify any trends in predicting those participants who are most likely to have improvement in language function at study end (e.g., age, gender, baseline function).

10.3 Sample Size Determination

The primary objectives of this study are to: 1) establish feasibility of an RS-tDCS and word naming practice in an adult PPA population, and 2) collect preliminary efficacy data to inform a grant application and sample size calculations for a large controlled trial.

A total of 30 adult PPA participants will be enrolled in the study based on the estimated number of eligible patient contacts across the study period.

10.4 Description of Statistical Methods

For Objective 1, feasibility, individuals will be categorized as “compliant” based on percentage of study completion. Compliance with the interventions will be assessed by summarizing the distributions of numbers and proportions of

completed sessions. Descriptive analyses will be completed to identify any trends in predicting those participants who are most likely to be compliant (e.g., age, gender, baseline function).

For Objective 2, preliminary efficacy, we will convert performance at baseline and study end across study measures (QAB, BNT, COWAT, self-report questionnaires). Change in scores, indicating change following intervention, will be calculated for each compliant participant (defined as above). Descriptive analyses will be completed to identify any trends in predicting those participants who are most likely to have improvement in language function at study end (e.g., age, gender, baseline function) as well as corresponding degree of use of the RS-tDCS and word naming practice with magnitude of benefit.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and subject files. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black or blue ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. 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.

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 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable NYU IRB regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Posting of Clinical Trial Consent Form
N/A

13.4 Participant and Data 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.

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.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities
Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original

entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

The self-reported questionnaires will be administered through REDCap survey function providing access to secure online questionnaires that can be completed from any browser. All study data collected through REDCap will be printed and stored in locked cabinet only accessible to the research staff at 222 E 41st Street, 10th Floor.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents and reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

15 Study Finances

15.1 Funding Source

This study is not currently funded.

15.2 Costs to the Participant

Participants will not be responsible for any costs related to the research procedures involved in this study.

15.3 Participant Reimbursements or Payments

Participants will be compensated $300 for completing the study ($100 Baseline; $200 at treatment-end visit).

16 Study Administration

16.1 Study Leadership

Leigh Charvet, Ph.D.
Dr. Charvet is a professor of neurology and the Director of MS Research for the NYU Langone Health's MS Comprehensive Care Center, also directing the neuromodulation research program and clinical tDCS service. She has >25 years of clinical and research experience working with people living with MS. She has established a large research and clinical program using noninvasive brain stimulation with tDCS, and pioneered the development and validation of the remotely supervised, or RS-tDCS, tele-platform for interventions to be accessed by patients and research participants remotely. She has an extensive record of funding for investigator initiated clinical trials including those supported by the NIH, National MS Society, U.S. Department of Defense and other agencies. Dr. Charvet will be responsible for overseeing the completion of the research project, building on her extensive background in MS clinical trials, tDCS, and telerehabilitation. She will oversee all aspects of the study including procedures, recruitment, and tDCS intervention. She will coordinate the full study team with frequent contact and weekly meetings to successfully complete this trial. She will work with the study team to operationalize the study procedures and train all personnel in the procedures. She will lead participant recruitment, database creation, and data entry. She will monitor recruitment, and take the primary scientific responsibility for completing progress reports as well as presentation and publication of the study results.

Amy Vogel-Eyny, Ph.D., CF-SLP
Dr. Vogel-Eyny is a post-doctoral fellow in the NYU Langone MS Comprehensive Care Center with clinical and research experience with a variety of patient populations and with the use of tDCS as an adjuvant to behavioral treatment. Dr. Vogel-Eyny will serve as a consultant for the development and administration of the word naming practice and train study staff to administer and score this exercise.

Eric McConathey, M.A.
Eric McConathey is a Senior Research Coordinator in the NYU Langone MS Comprehensive Care Center with experience working with various clinical and research populations and various types of non-invasive brain stimulation. He will oversee the collection of data, and its recording and interpretation. Eric will be involved in the recruitment and consenting processes, administration of language assessments, daily RS-tDCS usage, and administration of word naming practice under the supervision and training of Dr. Vogel-Eyny.

Giuseppina Pilloni, Ph.D.
Dr. Pilloni is a biomedical engineer with the therapeutic applications of noninvasive brain stimulation and tDCS devices, with extensive and international experience working in MS rehabilitation. She will provide biomedical engineering expertise for all equipment use. Drs. Pilloni and Charvet will work with the vendors to ensure ongoing technical and equipment support and guidance for the study.

Lauren Krupp, M.D.
Dr. Krupp is the medical monitor for the NYU Langone tDCS program including all tDCS research studies and the clinical service program. She will participate in routine safety data monitoring and address issues related to tolerability as experienced during the trial.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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19 Schedule of Events

	Screening	Baseline	RS-tDCS sessions + word naming practice	Treatment End
			1-20	
Study Team Procedures				
Obtain medical history	X			
Obtain written informed consent	X			
tDCS Device Training/tolerability test		X		
Assessments				
Word naming practice			X	
Exploratory cognitive and symptom measures				
Language Assessment		X		X
Self-report Questionnaires		X		X
Safety Reporting				
AE reporting			X	