Protocol Title: Evaluating Anodal tDCS Preceding Aphasia Therapy

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Introduction

Aphasia is a communication deficit resulting from a brain injury or a stroke. It can affect one's ability to speak, understand, read, and write, though the hallmark symptom is a word-finding deficit. It is estimated that there are 80,000 new cases of aphasia per year in the United States, and approximately 1 million people in the United States today, suffer from aphasia (1). Traditional aphasia therapy focuses on both training of compensatory strategies for communication and mass practice of communication skills with hierarchical cueing from an SLP (Speech and Language Pathologist). For example, an individual with aphasia may learn to point to pictures on a communication board to express wants/needs or practice simple object naming with progressively fewer and less supportive verbal or gestural cues. These therapy techniques have remained relatively unchanged since the early 1990's. Recent stroke rehabilitation research has suggested that non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), may augment the benefits of traditional rehabilitation by modulating cortical activation, and priming the cortex for improved motor and cognitive recovery. tDCS combined with aphasia therapy has been shown to improve naming, verbal fluency, repetition, and linguistic cohesion for conversational narratives (2-10).

However, debate remains over the optimal parameters for cortical stimulation including intensity, location, polarity (anodal/cathodal), and timing. Most research on tDCS and language therapy has applied neurostimulation during language treatment (2, 4, 5, 8, & 10). However, others, using tDCS in patients recovering motor function after a stroke, have found the greatest improvement when anodal tDCS preceded robotic hemiplegia training (11). In a pilot study, we want to test the hypothesis that anodal tDCS delivered before language treatment will affect the naming ability in patients with aphasia after chronic stroke (greater than 6 months from acute injury).

Specific Aims

SPECIFIC AIM 1: To evaluate whether anodal tDCS preceding aphasia therapy significantly improves picture naming in individuals with post-stroke aphasia.

In patients with chronic post-stroke aphasia, we will use a within-subjects repeated-measures design, to evaluate the effects of computerized mass practice audiovisual word-picture matching therapy (5 day/week x1 week) preceded by 20 min of anodal tDCS. Functional improvement will be determined by changes in naming accuracy on trained and untrained word lists.

We are aware that naming is one aspect of the language impairment that may occur after stroke. Thus, we will also measure other aspects of language function, so that if naming does not change there will be additional tests of the hypothesis.

SPECIFIC AIM 2: To compare naming performance between intervention groups (tDCS and sham stimulation).

We will use a single-subject cross-over design to compare two tDCS conditions (1mA anodal vs. sham). Treatment sessions will occur for five consecutive days per condition, with one week between conditions (3 weeks total). Functional improvement will be determined by changes in naming accuracy on trained and untrained word lists.

If neuromodulation (tDCS) preceding treatment is effective for promoting robust recovery in naming ability , as it has demonstrated for motor recovery in patients with chronic stroke and hemiplegia, then we expect the improvement in naming accuracy to be greater following anodal tDCS compared with sham tDCS.

These pilot results will support or not the continued investigation of novel non-invasive neuromodulation techniques.

SPECIFIC AIM 3: To compare naming performance between severity groups (high vs. low functioning aphasia as determined by admission Western Aphasia Battery scores (WAB)).

Preliminary Data

There is an increasing understanding of the mechanism of action of tDCS. Further and most importantly, there is clinical demonstration of its safety and efficacy (20-25). tDCS modulates the excitability of a targeted brain region non-invasively by altering neuronal membrane potentials (12, 13). Hence this technique will increase or decrease the excitability of neurons in a brain area, depending on electrode placement, and can thus be used to determine whether activity in a particular brain region can affect a specific motor/cognitive function. tDCS does not cause neurons to fire, but alters the likelihood that neurons will fire by hyperpolarizing or depolarizing brain tissue. The prolonged effects of tDCS have been attributed to long-term potentiation (LTP) and long-term depression (LTD) (14-19). In animals, anodal cortical stimulation of 5-30 minutes has been shown to cause excitability increases lasting for hours after the stimulation, primarily through modulation of the resting membrane potential (26, 27). In humans, 13 minutes of tDCS resulted in an increase in excitability up to 150% and lasting 90 minutes (28). Research with tDCS has revealed that anodal stimulation can induce transient (on the order of 30 minutes) improvements in performance on cognitive, motor and linguistic tasks (2, 29, 30). For example, anodal tDCS to dorsolateral prefrontal cortex elicited an improvement in working memory (31); stimulation to primary motor cortex improved motor learning and motor control (18, 30); tDCS delivered to primary motor area or to visual area V5 induced improvements in visuo-motor coordination (32); anodal stimulation of fronto-polar regions improved probabilistic classification learning (29); and left prefrontal cortical stimulation lead to increased verbal fluency (9). Cathodal stimulation decreases cortical excitability in humans - i.e., affected neurons will be less likely to fire (19). So there is gathering evidence that attests to the efficacy and safety of tDCS both in healthy participants and in individuals with stroke. The potential for therapeutic applications in stroke recovery is obvious.

More recently, tDCS has been applied in combination with post-stroke aphasia therapy and yielded promising results including improved word-retrieval, repetition, verbal fluency, and better cohesion of verbal narratives. Marangolo et al. reported that for individuals with aphasia, 1mA of anodal tDCS to the left inferior frontal gyrus during intensive language training significantly improved verbal repetition (8) and expression of cohesive ties (pronouns, ellipses, word repetitions, conjunctions) during a verbal narrative task (10). Baker, Rorden & Fridriksson demonstrated that in individuals with post-stroke aphasia, 1mA of anodal tDCS to the left frontal

cortex administered during 5 consecutive days of computerized anomia therapy significantly improved naming accuracy as compared to a therapy-matched sham stimulation condition (4). Interestingly, they found that participants with the greatest improvement in naming accuracy were those with intact perilesional tissue closest to the activation site of the tDCS anode. Moreover, Fiori et al. (2011) showed that 1mA of anodal tDCS over left Wernicke's area significantly improved both reaction time and non-word verbal learning in healthy controls, and real word retrieval individuals with aphasia (2). Response accuracy and reaction time improvements of the aphasic group remained robust at follow up (1 and 3 weeks post), indicating potential for long-term recovery. Overall, these recent studies specifically on recovery of aphasia suggest that tDCS in combination with standard therapy is a potentially powerful tool for enhanced recovery of language in individuals with aphasia.

However, stimulation parameters vary substantially between aphasia studies, warranting further investigation. Specifically, timing of stimulation may play a key role in performance. While some investigators demonstrated significant naming accuracy improvements in individuals with aphasia who received 1mA of anodal tDCS during intensive language therapy (2, 4), others showed that the greatest improvement occurred when anodal tDCS preceded training (11).

Based on these results, the present study will examine the effect of anodal tDCS before language treatment using an approach that has previously been used concurrently with language treatment in order to determine the most effective timing parameters for stimulation applied with aphasia interventions (4).

Research Design and Methods

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. ≥ 18 years of age
2. First single focal unilateral left hemisphere lesion with diagnosis verified by brain imaging (MRI or CT scans) that occurred at least 6 months prior
3. Pre-morbidly right handed
4. Pre-morbidly fluent English speaker
5. Cognitive function sufficient to understand the experiments and follow instructions (per interview with Speech Pathologist)
6. A baseline Aphasia Quotient score between 10 to 94 out of 100 points on the Western Aphasia Battery (neither completely without language comprehension/expression nor fully recovered from aphasia).

Exclusion Criteria:

1. Ongoing use of CNS-active medications
2. Ongoing use of psychoactive medications, such as stimulants, antidepressants, and anti-psychotic medications
3. Presence of additional potential tDCS risk factors:
    - Damaged skin at the site of stimulation (i.e., skin with ingrown hairs, acne, razor nicks, wounds that have not healed, recent scar tissue, broken skin, etc.)

- Presence of an electrically, magnetically or mechanically activated implant (including cardiac pacemaker), an intracerebral vascular clip, or any other electrically sensitive support system
- Metal in any part of the body, including metal injury to the eye (jewelry must be removed during stimulation)
- A history of medication-resistant epilepsy in the family
- Past history of seizures or unexplained spells of loss of consciousness during the previous 36 months

4. Pregnancy in women, as determined by self-report

Visit Schedule

In this pilot study, 24 participants will be accepted from our referral sources in the department of Neurology and Physical Medicine. There will be 2 measurement periods before the training starts, separated by 3-14 days in order to establish baseline word-finding performance on selected trained and untrained word lists. Following the lead-in period, subjects will participate in a cross-over design training period to compare the two tDCS conditions (1mA anodal vs. sham). The training portion of the study will occur over a total of 3 weeks. During that time, subjects will attend five consecutive, 60-minute training sessions under treatment condition one (anodal vs. sham tDCS), followed by a 1 week rest interval, and then another five consecutive sessions of training under treatment condition two. Order of training word lists and tDCS stimulation condition will be counterbalance across participants. Subjects will undergo four additional evaluations throughout the course of the study, two of which will occur immediately after each of the training conditions (discharge), and the other two of which will occur 1 week after each training condition (follow-up). All study procedures will be administered or supervised by the research coordinator or another licensed Speech-Language Pathologist. All visits will be conducted in the clinical robotics and non-invasive brain stimulation suite at the Feinstein.

<u>Lead-in Period</u>

- Week 1, Visit 1 (approximately 60 minutes)
  - Baseline outcome measures
  - Medical screening
  - Consent
- Week 2, Visit 2 (approximately 60 minutes each)
  - Baseline outcome measures

<u>Training Period Phase I</u>

- Week 3, Visit 3-6 (approximately 60 minutes)
  - 20 min of stimulation condition 1 (sham or anodal tDCS) and 20 min of computerized word-picture matching therapy
- Week 3, Visit 7 (approximately 90 minutes)
  - 20 min of stimulation condition 1 (sham or anodal tDCS) and 20 min of computerized word-picture matching therapy
  - Condition 1 discharge outcome measures

Follow Up Testing Phase I

- Week 4, Visit 8 (approximately 60 minutes)
    - Condition 1 follow-up outcome measures

Training Period Phase II

- Week 5, Visit 9-12 (approximately 60 minutes)
    - 20 min of stimulation condition 2 (sham or anodal tDCS) and 20 min of computerized word-picture matching therapy
- Week 5, Visit 13 (approximately 90 minutes)
    - 20 min of stimulation condition 2 (sham or anodal tDCS) and 20 min of computerized word-picture matching therapy
    - Condition 2 discharge outcome measures

Follow Up Testing Phase II

- Week 6, Visit 14 (approximately 60 minutes)
    - Condition 2 follow-up outcome measures

Schedule Chart

	Screen 1	Screen 2	Tx Condition 1		Cond 1 FU	Tx Condition 2		Cond 2 FU
	Visit 1	Visit 2	Visit 3-6	Visit 7	Visit 8	Visit 9-12	Visit 13	Visit 14
Informed Consent	X							
Medical Hx	X							
Medical FU		X						
Demographic Info	X							
Inclusion Criteria	X							
Neurological Exam	X							
Medication check	X							
Outcome Measures	X	X		X	X		X	X
tDCS and Aphasia tx			X	X		X	X	

Clinical Outcome Measures

Naming Probes (Primary Measure):
Picture naming accuracy will be assessed across two word lists, which were developed in a previous study (4). Each word list is comprised of a total of 75 trained and untrained nouns, which are controlled for word-frequency, semantic content, and word length, and depicted with color pictures presented on a laptop. Subjects will be provided with a different word list for each condition (sham vs. anodal tDCS), and asked to name each picture as soon as they see it. Responses will be audio/visually recorded for later transcription and scoring by an SLP. The first complete response will used to determine the accuracy score. The outcome measure will be change in naming accuracy of trained items (task learning) and untrained items (learning generalization) in each condition.

Aphasia Battery (Secondary Measures):
A set of brief subtests from larger aphasia batteries will be used to asses changes in verbal expression and fluency in subjects with chronic expressive aphasia. Audio/Video recordings will be made of speech-language assessments for review and scoring by approved clinicians.

-"Diadochokinetic Rate" and "Increasing Word Length," subtests of the Apraxia Battery for Adults (ABA-2): The ABA-2 is a valid and reliable measure of changes in motor speech across isolated speech sounds, multisyllabic utterances, and connected speech samples. Together, these subtests take approximately 5 minutes to administer and derive an apraxia impairment profile score (42, 45, 46).

-Generative Naming: Generative Naming is a commonly used clinical measure of verbal fluency and semantic memory in individuals with aphasia. It has been used frequently in the tDCS literature as a sensitive metric of changes in verbal fluency (38, 39, 43).

-Philadelphia Naming Test short form (PNT): The PNT is a valid and reliable measure of changes in expressive naming across time in stroke patients with expressive aphasia. Performance on the PNT short form has been statistically correlated to PNT long form performance for individuals with aphasia (40, 41, 42).

-Connected Speech Sample including the "Cookie Theft" or "Birthday Party" picture descriptions: Connected speech samples are frequently used metrics of changes in rate, fluency, and language formulation in individuals with aphasia. Audio/visual recordings of naturalistic language samples allow for independent quantitative scoring of language function by clinicians (45, 46).

-"Symbol Cancellation" subtest of the Cognitive Linguistic Quick Test (CLQT): is a valid and reliable non-verbal, visual cancellation task. It is frequently used by clinicians in aphasia literature as a non-verbal control task of attention and visual memory (43).

-Western Aphasia Battery Revised (WAB-R): The WAB-R provides an aphasia quotient for type and severity of aphasia, and is commonly used in the aphasia literature. Changes of >5 points are clinically significant (42, 44, 45).

Transcranial Direct Current Stimulation (tDCS) Application:

Patients will sit in a comfortable chair and a plastic band will encircle the skull. An electrode – a flat 5X5cm plate – will be ensheathed in a disposable cotton sponge and held in place by the band. The reference electrode (cathode) covered by the pad will be placed on the right shoulder and another electrode (anode) will be placed over Broca's area (left posterior inferior frontal gyrus). To locate the optimal cortical region of the left frontal cortex to be stimulated by the anode electrode, tDCS current modeling of each subject's MRI will be performed.

A 1mA current will be delivered using the surface rubber-carbon electrodes ($35cm^2$) with surrounding saline soaked sponges (0.9% NaCl) by a battery driven, constant current stimulator (maximum output 2mA) (51). Participants will receive stimulation for 20 minutes while seated (prior to language training), with the anode over the left frontal cortex and the cathode on the right shoulder. Sham tDCS: comparable set-up to real tDCS, 30 seconds real current ramping to 1mA at commencement, then after 5 seconds a slow decrease but no current sustained for 20 minutes.

Computerized Anomia Treatment:
This self-administered computerized anomia treatment was reported on in a previous study, and demonstrated to be helpful in improving naming accuracy of individuals with aphasia (4).
Subjects are asked to perform a 20-minute picture-word matching task following receipt of either sham or anodal tDCS.

Randomization
A single-subject cross-over design will be used to compare two tDCS conditions (1mA anodal vs. sham). The order of anodal or sham stimulation will be counterbalanced across participants, and determined using a random number generator.

Blinding
This is a double blind study. The tDCS device will be covered such that the administrator will code each stimulation condition as either switch "up" or switch "down," but will remain blinded to which code is anodal vs. sham stimulation. In this way, all investigators interacting with patients will remain unaware of stimulation condition. For the sham condition, the stimulation automatically ramps down after 30 seconds because the perceived sensation of tDCS on the skin has been reported to fade after this period (21). Consequently, participants will also stay blinded to stimulation condition.

Statistical Considerations and Data Analysis

SPECIFIC AIM 1: To evaluate whether anodal tDCS preceding aphasia therapy significantly improves picture naming in individuals with post-stroke aphasia.

Methods to address specific aim 1: A Wilcoxon signed-rank test will be used to compare naming accuracy scores pre and post anodal tDCS condition across participants.

SPECIFIC AIM 2: To compare naming performance between intervention conditions (tDCS and sham stimulation).

Methods to address specific aim 2: If neuromodulation preceding treatment is effective for promoting recovery in language impairment, as it is in robotic hemiplegia treatment, we expect the improvement in naming accuracy to be greater following anodal tDCS compared with sham tDCS. This will be examined with a 2x2 repeated measures ANOVA for both treated and untreated items with stimulation type (A-tDCS,S-tDCS) and time (T1, T2) as factors.

SPECIFIC AIM 3: To compare naming performance between severity groups (high vs. low functioning aphasia as determined by admission Western Aphasia Battery scores (WAB)).

Methods to address specific aim 3: This will be examined with a 2x2 repeated measures ANOVA with change in naming performance in each stimulation condition (change in naming performance A-tDCS vs. S-tDCS) and severity level (high vs. low functioning aphasia).

Protection of Human Subjects

RISKS TO SUBJECTS

Human Subject Involvement and Characteristics: We anticipate enrolling 12 human subjects. Inclusion and exclusion criteria are stated above in the Research Design and Methods section.

Sources of Material: Sources of research material will be the hospital records providing demographic and medical information including CT or MRI imaging studies, and clinical examinations performed at outpatient facilities run by the Department of Physical Medicine and Rehabilitation of the North Shore University Hospital (NSUH) and LIJ Medical Center (LIJMC), or copies of medical records from outside hospitals provided by participants.

Potential Risks:
tDCS Risks: tDCS is a safe technique that poses a non-significant risk to participants. The safety of this technique has been addressed and tested by multiple researchers (16, 18, 20, 33-34) who have concluded that tDCS, as applied in a manner similar to our proposed protocol has no long-term negative side effects. More than 30 research studies involving hundreds of participants have been published using tDCS. Hundreds more participants have undergone tDCS for unpublished pilot research. No undesirable or long-lasting effects have been reported, nor have any participants reportedly abandoned a study due to discomfort.

Researchers at the National Institute of Neurological Disorders and Stroke (NINDS) conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103) (20). No negative effects were identified. Nitsche and colleagues (2004) found no measurable structural changes in brain tissue due to tDCS (23). Additionally, studies have shown that tDCS can be used safely in stroke patients (11, 18, 34-37). Thus, a growing body of research from different laboratories has shown that tDCS is a safe, non-invasive and painless technique for modulating neural excitability, with measurable but only transient effects. The protocol described here uses stimulation levels that fall well within safety limits established by basic research investigating neural tissue damage, as well as

numerous studies applying tDCS with human participants (22-24). tDCS has the potential to cause erythema – redness of the skin that is uniform or mottled around the area of stimulation. The reddening has been found to be transient for level of stimulation proposed in this protocol (20-21).

Confidentiality Risk: One additional risk concerns the risk to confidentiality incurred with any collection of medical data.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent: Stroke subjects who meet inclusion criteria and do not meet exclusion criteria will be recruited by consenting professionals through the Department of Physical Medicine and Rehabilitation of NSUH and LIJMC. Recruitment will be done with direct contact and flyers.

Northwell Health Health physicians and clinicians who have appropriate patient populations will be made aware of the research study protocol and procedures, and given an overview of the study through contacts with the study personnel. These clinicians will identify potential study participants. If the patient expresses interest in participation, the clinician will either: 1.) provide the patient with the study coordinator's contact information or 2.) provide the patient's contact information to study personnel.

Investigators may contact (or be contacted by) a potential subject or subject's LAR/next-of-kin by telephone to discuss participation in this research protocol. The investigator will provide the subject/LAR/next-of-kin with all the information contained in the written consent form. The investigator will answer any questions regarding the research and give the subject/LAR/next-of-kin ample time to consider participation in the study which may require a follow-up phone conversation.

After a discussion about the study with a potential subject and/or a potential subject's legally authorized representative (LAR)/next of kin, interested parties will be given a copy of the consent form by one of the study investigators. The investigator will review and explain the consent form. All information about the study will be provided. Ample time will be given for individuals to ask questions regarding participation and to have questions answered prior to signing the consent form. If so desired, those interested will be given a copy of the consent form so that they may have the opportunity to discuss participation further with family and/or advisors. Only those investigators listed in the study protocol will obtain informed consent. If an individual chooses to enroll, the consent form will be signed before participation begins. Once an individual joins the study and informed consent is obtained, the subject will receive a signed copy of the consent form. The subject may withdraw from the study at any time without repercussions to subsequent care.

If the patient is awake, alert, and oriented to person, place, and time, and demonstrates appropriate cognitive and communicative abilities as determined by the study coordinator or PI, the patient will be deemed to have the appropriate capacity to consent; however, given that borderline cognitive dysfunction and/or aphasia may not be easily distinguishable, the patient's

LAR/next of kin will be routinely included when consent to participate is being obtained for all subjects.

If it is determined that a patient is unable to consent for him/herself, due to a lack of capacity or lack of comprehension, consent will be sought from the patient's LAR/next of kin. Assent of the adult subject with LAR/next-of-kin will be obtained as appropriate. If such a subject regains his/her ability to make healthcare decisions, he/she will be given the opportunity to provide consent. This consent will be documented using the Addendum to Consent by Research Proxy for Continuing Participation in a Research Study form.

If the patient provides the consent delegate with assent to participate in the research but, due to a physical disability, is unable to sign the consent form, the patient will provide verbal consent and two witnesses and the patient's LAR/next of kin will sign the document affirming their presence during the consent process and the patient's physical disability as reason for an absent signature.

Protection Against Risk:

Protection against tDCS-related risks: If any redness is apparent where the electrodes were placed, a cold compress will be offered to the subject. We will monitor subjects continually during the stimulation period, and will be in constant contact with the subjects. The study can be immediately stopped at the subject's request.

Protection of Confidentiality: To protect subjects' confidentiality, each subject will be assigned an ID number, and all data will be stored with the subject ID number only and not the subject's name. Data will be stored on a password-protected computer and on Feinstein's data server, REDcap. The *Feinstein Institute for Medical Research* will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biostatistics Unit of the *Feinstein Institute for Medical Research*. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at the Feinstein and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Northwell Health researchers by both our Clinical Research Service, Research Compliance Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports 965 active institutional partners and other institutions in 78 countries (www.project-redcap.org)Subject charts with medical history and assigned subject numbers will be kept in locked file cabinets stored at the Feinstein robot suite. Access to charts will be granted only to study investigators. Charts will be kept confidential and will not be shared with any third parties without permission from the subject. Any study data containing PHI that is transferred between investigators at Feinstein and collaborating institutes will be shared via encrypted email or encrypted storage drives.

Data and Safety Monitoring: To protect both the integrity of the data and the safety of all study participants, study data review in aggregate will occur every 4 months by the Principal Investigator.

POTENTIAL BENEFIT TO SUBJECTS AND OTHERS

The risk/benefit ratio is very low in the proposed study due to the established safety of the protocol and to the great potential for using the findings to improve rehabilitation methods.

SCIENTIFIC VALUE

The results of this study may help to improve rehabilitation of post-stroke aphasia.

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