Scientific Review: Method 3

Study Title: *Use of anodal transcranial direct current stimulation (a-tDCS) to DLPFC to influence naming in patients with non-fluent aphasia: a feasibility and safety study.*

Reviewer 1
Name: Bernadette Gillick, PhD, MSPT, PT Affiliation: University of Minnesota Program in PT

Review 2
Name: James Carey, PhD, PT Affiliation: University of Minnesota Program in PT

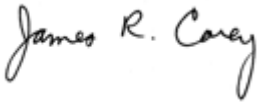
Reviewer 3 (optional)
Name: Affiliation:

Date of Review: 11.3.14 (Final) **Method of Review: Collaborative via email**
Discussion: At this time of 3 rd review, the proposal is deemed satisfactory in its science.

Decision: Approved.

Signatures:

_____ _____11.4.14_____
Reviewer 1 **Date**



_____ _____11/4/14_____
Reviewer 2 **Date**

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Reviewer 3 (optional) **Date**

Scientific Assessment: Method 3

Study Title: *Effects of anodal transcranial direct current stimulation (a-tDCS) on naming in patients with non-fluent aphasia.*

PI: *Sharyl Samargia, PhD CCC-SLP*

Co-investigator: *Naomi Hashimoto, PhD CCC-SLP*

- **Is the rationale for the study clearly stated and is the rationale scientifically sound?**

The emerging evidence of the relationship between working memory (WM) and naming offers a unique opportunity to investigate the effects of upregulation of WM systems and the effect on naming in nonfluent aphasia. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation tool that presents a low current that induces bi-directional polarity-dependent changes in the cortex to facilitate focal, prolonged shifts in cortical excitability at or around the time stimulation is provided [1, 2]. Anodal tDCS (a-tDCS), in which the positively charged electrode is placed over the targeted cortical region, has been shown to increase cortical excitability (upregulation), similar to long-term potentiation (LTP)[1-5]. Combining a-tDCS with behavioral-based approaches has been suggested to enhance the learning process and increase the likelihood of retention[6]. Although there is no specific neurophysiologic evidence to identify suppression of dorsolateral prefrontal cortex (DLPFC) in participants with aphasia, it has been implicated in naming deficits due to its role in working memory. tDCS has been applied to the DLPFC to target working memory[7-10], to date, there have been no investigations using a-tDCS to the DLPFC to influence naming skills in non-fluent aphasia. The overarching goal of this study is to explore the relationship between WM and naming by investigating the effects of a-tDCS to left DLPFC on naming accuracy and naming reaction times (RTs) in non-fluent aphasia. The primary purpose of this study is to 1) establish feasibility and safety of applying a-tDCS to the left DLPFC in patients with Broca's aphasia combined with behavioral naming treatment.

- **Are the aims and corresponding hypothesis clearly stated?**

Aim 1: Determine feasibility and safety of applying a-tDCS to the left DLPFC in Broca's aphasia. Two conditions: 1)a-tDCS (2mA for 20 minutes) will be applied over the left DLPFC followed immediately by behavioral naming therapy and 2) sham tDCS followed immediately by behavioral naming therapy will be presented to participants with non-fluent aphasia. *Hypothesis 1:* no adverse events will be reported during or following this treatment and all participants will complete the study.

Aim 2: Identify effectiveness of a-tDCS to the left DLPFC combined with behavioral naming treatment in Broca's aphasia and establish a sample size for future investigations of this nature. A small sample size will be used in this study to investigate effectiveness of the use of a-tDCS to the left DLPFC with behavioral therapy to target naming in non-fluent aphasia. *Hypothesis 2:* Improvements in working memory, naming reaction time and naming accuracy will be observed after the real a-tDCS condition but not after the sham a-tDCS condition.

- **Is the primary outcome (and secondary outcomes, as appropriate) clearly defined?**

Primary outcomes include: naming accuracy on treated and control items, naming RTs on treated and control items, performance on WM tasks, and motor speech tasks.

- **Are there adequate preliminary data in the literature (or from the investigator) to justify the proposed research? Has an adequate literature review been done to support this study?**

WM systems are short-term, temporary stores that are activated when active manipulation of items is necessary[20]. It could be argued that all linguistic tasks invoke WM systems since the execution of any linguistic task requires the ability to maintain activation of a representation until the targeted linguistic process is complete. Indeed, the close relationship between language and WM is represented in many WM models[11-13]. Over the past few decades, there has been increasing recognition that aphasia is frequently accompanied by deficits in WM systems. Furthermore, such deficits adversely impact linguistic performance in aphasia. Accordingly, treatment protocols are being developed on the premise that treatments aimed at improving WM systems will improve linguistic function in aphasia[14, 15]. While a variety of WM treatment protocols have been designed to improve linguistic processes such as oral reading, repetition, or comprehension abilities in aphasia, there are no such studies in the area of naming. Yet, one particular WM component, subvocal rehearsal processes[11, 16], may play a crucial role in naming abilities in aphasia. Subvocal rehearsal processes are activated when verbal memory traces must be refreshed. Such processes become vital in cue-based protocols[17-21] where the individual is asked to self-generate cues needed to increase lexical access to the object name. Within this context, it may be that subvocal rehearsal systems might be crucial during picture naming processes as it functions to preserve and refresh information, facilitating convergence of activation onto targeted representations. This becomes a useful compensatory strategy when there are lexical access and retrieval failures. However, the ability to engage in subvocal rehearsal processes are likely deficient in individuals with aphasia[14 15], which impacts not only immediate treatment effects, but also long-term treatment effects since cue self-generation as a compensatory strategy would be limited.
The application of a-tDCS to the language regions in combination with behavioral-based approaches has resulted in improved language outcomes in individuals with aphasia [22-26]. In addition, a-tDCS applied to the left DLPFC has resulted in improved performance on WM tasks in healthy individuals [27], individuals with Parkinson's Disease [7] and stroke [28]. a-tDCS is ideally suited to upregulate the left DLPFC and may potentially activate subvocal rehearsal processes needed in order to improve self-generation of cues during naming. However, there have been no investigations to date using neuromodulation techniques to the DLPFC to target naming skills in aphasia.

- **Is the question or hypothesis being tested providing important knowledge to the field?**

The findings from the proposed study will lay the foundation for a larger clinical trial which will in turn have a significant impact on individuals with aphasia given that naming deficits are a common symptom in this population. As the presence of naming deficits has a negative relationship to emotional well-being and functional communication [29-33], treatment that improves naming deficits will positively influence quality of life in many of these individuals. The approach taken to remediate naming deficits in aphasia is to treat impaired WM systems

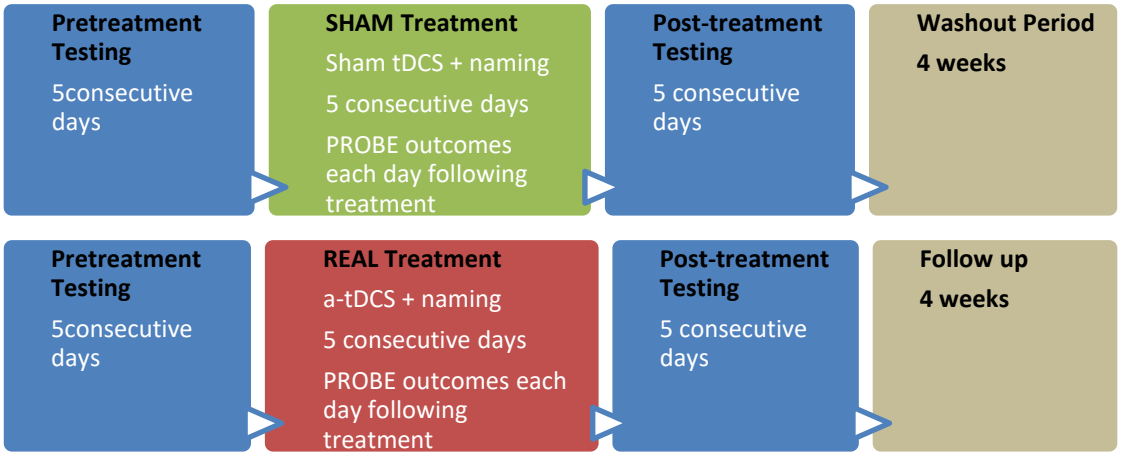
on the premise that certain cognitive processes underlie linguistic functions in aphasia. This approach represents a departure from most behavioral-based naming treatment approaches, but reflects a growing recognition that WM systems in individuals with aphasia impact linguistic performance [14, 34]. The addition of a-tDCS as a neuromodulation tool to increase cortical excitability (upregulate) the working memory center to target naming is a novel approach in aphasia. These findings, , will provide valuable information regarding the role WM plays in naming and the potential benefit of using neuromodulation to the DLPFC to influence naming in aphasia.

- **Is the design of the study appropriate for the questions that are posed?**

Treatment Design:
A single subject cross-over design with a 4 week wash out period will be used. Two treatment conditions will be presented. The sham (SHAM) condition will consist of presentation of sham tDCS for 20 minutes followed by behavioral naming treatment. The real treatment condition (REAL) will consist of 20 minutes of a-tDCS to the left DLPFC followed by behavioral naming treatment. The length of behavioral naming treatment will depend on how long each participant takes to go through the treatment stimuli twice. A SHAM-REAL sequence will be used across all participants. Although order effects may be introduced using the same sequence across participants, the small number of participants makes it difficult to interpret any data that comes from using a counterbalanced presentation of treatment.
Treatment will be provided over five consecutive days. A minimum of a one-month washout period will be provided between the two conditions (Figure 1). Prior to initiating the REAL treatment condition, the naming RTs obtained on the second word list during the pre-treatment testing period (prior to the initiation of the SHAM condition) will be compared to the naming RTs obtained after the washout period. RTs will be analyzed to ensure that no lasting treatment effects remain after the SHAM condition. If performance on naming RTs is +/- 1 standard deviation from the individual's benchmark mean, the REAL treatment condition will begin. If performance on naming RTs is > +/- 1 standard deviation from the individual's benchmark mean, REAL treatment will be postponed until the mean RTs fall within +/- 1 standard deviation of the benchmark. Periodic checks will be conducted weekly to identify when to begin REAL condition. Once there are minimal differences between naming RTs on the second word list, the REAL treatment will be initiated.

Outcome measures:
Two different word lists will be generated; a different list will be used for each treatment condition to control for exposure and learning effect.Pretreatment testing outcome measures will be recorded for 5 consecutive days for each outcome measure including: 1) naming accuracy 2) naming RTs on both word lists 3) performance on motor speech tasks and 4) performance on working memory tasks. Stability of baseline performance, defined as no more than 20% difference between scores, will be obtained in five consecutive sessions. In addition, outcome measures will be obtained immediately after each treatment session. Five maintenance outcome measures will also be obtained upon completion of treatment. These sessions will take place at the Clinical Translational Science Institute (CTSI) on Delaware Street on the University of MN campus. An adverse events questionnarie will also be given after each treatment session as a mechanism of participants reporting any discomfort.

Figure 1. Treatment Schedule



tDCS Protocol.

Treatment sessions will take place at the University of MN Clinical Translational Science Institute. Each participant will be seated comfortably in a chair. A swim cap will be placed on the participant's head to identify cranial landmarks for accurate electrode placement. The area referred to as F3 by the International 10/20 system for electroencephalogram electrode placement[35] has been established as the optimal location for targeting the left DLPFC[8, 9, 28, 36]. The F3 region will be located by marking the vertex (the midpoint between left and right tragus and midpoint between nasion and inion), measuring the head circumference. When these measurements are entered into the Beam F3 Locator Software[37], additional values are provided to reliably identify the location of F3. Once F3 has been established, two saline soaked surface sponge electrodes (35^{2}cm) will be prepared and placed. For optimal anodal stimulation to the DLPFC, the anode will be placed over F3 and the cathode will be placed over the right supraorbital region[7-9, 27]. A current of 2mA will be delivered for 20 minutes [7] by a multichannel transcranial current stimulator (Starstim, Neuroelectrics Corporation; Cambridge, MA). a-tDCS will be applied before and during behavioral treatment in the design specified below.

Behavioral-Based Naming Treatment Protocol.

Stimuli. Eighty black-and-white line drawings will be obtained from on-line clip art websites. Picture names will be normed using five to ten English-speaking volunteers who will be asked to provide the names of the pictures. Cues words will be paired with the pictures if the words represent an associative or thematic relationship. Therefore, the words will be chosen that represent a concrete attribute (e.g., the picture, SHARK, is paired with the cue word *teeth*), location (e.g., the picture, SHARK, is paired with the cue word *ocean*), and either function or category (e.g., the picture, SHARK, is paired with the cue word, *fish*). The selection criteria for choosing these particular attributes is based on a classification criteria of thematic relations [38]. Moreover, there is empirical evidence that that associative relations would prove beneficial in a naming treatment paradigm [39]. Commonly used phrases (e.g., *great white shark*) or compound words (e.g., *bluefin shark*), synonyms or antonyms will be excluded. These cue words will be obtained from a semantic features normative database [40], which provides not only semantic

features information but categorical information as well. Two lists of 20-items will be created, which will be presented to each participant in order to avoid presenting the same list across the conditions. Pictures used in both lists will be balanced in terms of visual complexity and familiarity ratings. Words used in all conditions will be balanced in terms of lexical frequency and word length. Familiarity ratings will be obtained from a normative database[40]. Visual complexity ratings will be also obtained from a group of 20 individuals using the instructions and rating scales as reported in Snodgrass and Vanderwart's[41] article. The CELEX database [42], will be consulted to determine lexical frequency of the words (cues) used in the study. An additional 40 pictures will be selected for a control (untreated) list that will be used only during baseline and post-treatment testing. Performance on treated and untreated lists will be compared to determine treatment effects and possible generalization effects.

Naming Treatment Procedures. All participants will be provided the same protocol, which will highlight the process of rehearsing the cues associated with the picture name. Treatment sessions will last until each participant has gone through the treated items twice. To insure control during the protocol, a graduate student trained in the protocol will administer the treatment steps. She will be blinded to the objectives of the study and conditions that are being administered. Treatment sessions will be video recorded for reliability purposes. To insure that she is not aware of when tDCS is being administered, a screen will be in place between the tDCS machine and the treatment table. The protocol is provided in Table 1.

Table 1. Naming Treatment Protocol.

Steps Involved in Naming Treatment Protocol	
Picture Presentation	Participant will be asked to name the picture. If she/he is unable to provide the name within 10 seconds, the name will be provided.
Cue Presentation	Cues that accompany the picture will be presented. He/she will be asked to read each cue word as it is presented. If he/she is unable to read the word spontaneously within 10 seconds, he/she will be asked to repeat each word after the clinician.
Cue Rehearsal	Both picture and cues are taken away. Participant is asked to rehearse the cue words silently for 10 seconds.
Cue Self-Generation	Participant will be asked to generate all three cues. For each instance that the participant is unable to provide a cue within 10 seconds, the cues will be provided. Once the cues have been provided, the participant will then be asked to provide the picture name.
Picture + Cue Presentation	If the participant is unable to provide the name, the cues will be read, or if he/she is unable to read spontaneously, he/she will be asked to repeat after the clinician. If she/he is still unable to provide the picture name after the cue review, it will be provided.
Picture + Cue Review	Once the cues and picture are laid out on the table, the clinician will read each cue and name the picture. The participant will be encouraged to read/repeat with the clinician.

- **Have the validity and reliability of measures been established or are there methods proposed for establishing validity and reliability?**

Approximately 20% of each of the participant's behavioral treatment sessions will be observed by the co-investigator in order to obtain procedural integrity. Steps of the treatment protocol will be scored using a binary (+/-) coding system. Point-by-point agreement will be obtained. Reliability in scoring naming error types will also be obtained using a table that lists the most common aphasic naming errors, definitions and examples of each error type. Point-by-point agreement will be obtained.

- **Is the proposed subject population appropriate?**

Participants will be recruited via emails sent to Twin Cities metro area hospital and aphasia/stroke support groups. Potential participants will then be screened for eligibility for the study.

Screening. Potential participants will be seen for 2-3 sessions to undergo comprehensive cognitive-linguistic assessment to determine eligibility for the study. This assessment will take place within the participant's home to provide a comfortable, natural environment for the potential participant. Behavioral assessment measures will include the Western Aphasia Battery (WAB) [43] which will be used to obtain overall language function via the WAB Aphasia Quotient (WAB AQ), the Boston Naming Test (BNT) in order to obtain naming function, [44], Apraxia Battery for Adults (ABA-2) [45] in order to determine apraxia of speech severity, and working memory tasks to determine subvocal rehearsal processes and phonological short-term store abilities.

These participants must meet the following inclusionary criteria:

- a diagnosis of moderate-moderately severe non-fluent aphasia based on performance on the WAB (see above screening procedures).
- a diagnosis of moderate-moderately severe non-fluent aphasia based on performance on the BNT (see above screening procedures).
- a diagnosis of mild-moderate apraxia of speech (AoS) based on performance on the ABA-2 (see above screening procedures).
- completion of high school or GED
- normal or corrected-to-normal vision
- adequate hearing acuity for 1:1 conversational exchanges
- use of English as primary language
- a vascular lesion in the dominant left hemisphere, not in the region of the DLPFC verified by an MRI scan within six months of the start of the study.

These participants must also meet the following exclusionary criteria:

- no previous history of neurological- or psychiatric-based illnesses or disease, language or learning disabilities, or alcohol/substance abuse
- no history of seizures
- no metal implants in the head (except dental fillings)
- no lesion in the left DLPFC confirmed by MRI

- no current pregnancy

Individuals who meet the inclusionary/exclusionary criteria and who are still interested in participating will then be consented to participate in the research study. After four participants have been identified as eligible and consented for the study, recruitment will stop.

- **Are statistical considerations, including sample size and justification, estimated accrual and duration, and statistical analysis clearly described and adequate to meet the study objectives?**

Descriptive statistics such as naming percent accuracy, range of naming percent accuracy, number of cues generated independently, and rates of naming errors, will be collected. Although normally distributed data is not expected in this small sample size and in this population of participants, a Shapiro-Wilk test of normal distribution will be conducted to report the distribution. Single subject analysis techniques will be used such as visual inspection, graphical analysis and confidence interval comparison.

Aim 1. To address the feasibility and safety aim, the number and type of adverse events for each patient will be recorded and presented. In addition, the number of participants who failed to complete the study will be recorded and factors recorded. To the extent possible, the participants will be asked to continue to participate in the assessments to allow a consideration of intent to treat analysis.

Aim 2. Means and 95% confidence intervals will be plotted and used for comparison of naming RTs, working memory performance and motor speech performance across treatment conditions for each subject (Deng, et al. 2013). Naming accuracy performance will be analyzed using *d* statistics for lexical data to determine magnitude of treatment effect [46, 47]. The effect size will be interpreted using benchmarks proposed by Beeson and Robey (2006) for lexical retrieval treatments: small ES = 4.0, medium ES = 7.0, large ES = 10.1[46]. Naming RT mean and confidence intervals will be analyzed for changes within and across treatment conditions using visual inspection.

- **Are all the proposed tests or measurements requested necessary to answer the scientific question?**

Yes. The proposed measures will allow investigators to report the feasibility and safety of the use of a-tDCS The measures will also allow investigators to identify individual treatment effects of a-tDCS to left DPFC combined with behavioral naming therapy on naming in non-fluent aphasia and through visual inspection and graphical analysis, compare effects to sham treatment. Naming RT and accuracy are sensitive measures of the participant's retrieval and learning of treated items. Motor speech performance will allow us to track changes in motor planning and sequencing abilities, which can influence naming RT and naming accuracy. And, performance on working memory tasks will allow for investigation of the influence of WM on naming and to provide additional evidence that a-tDCS to the left DLPFC may influence WM in individual participants.

- **Are the investigators well qualified to conduct this study?**

Key Personnel

Name	Affiliation	Role
Sharyl Samargia, PhD CCC-SLP	University Wisconsin River Falls	PI

Dr. Samargia is associate professor in the Department of Communication Sciences and Disorders and will serve as the principal investigator for the project. Dr. Samargia has expertise in neurophysiologic mechanisms and neuromodulation in healthy and neurologic populations. She will provide rationale and guidance in the neurophysiologic mechanisms of tDCS and will administer tDCS to the subjects.

Name	Affiliation	Role
Naomi Hashimoto, PhD CCC-SLP	University of Wisconsin-River Falls	Co-investigator

Dr. Hashimoto is an associate professor in the Department of Communicative Sciences and Disorders. Dr. Hashimoto's research interest involves the examination of lexical-semantic deficits in individuals with aphasia. The deficits found in these individuals are interpreted within the context of a cognitive neuropsychology approach. Methodologies such as on-line measures and the more traditional assessment batteries are used to examine how various aspects of the lexical-semantic (word meaning) system operates in the brains of neurologically intact individuals and individuals with aphasia. She is the director of the Aphasia Research Laboratory at UWRF.

Name	Affiliation	Role
Teresa Jacobson Kimberley, PhD PT	University Minnesota Twin Cities	Mentor

Dr. Kimberley is an associate professor in the Programs in Physical Therapy and Rehabilitation Science and serves as a director of the Brain Plasticity Lab. Dr. Kimberley has expertise in neurophysiologic mechanisms and neuromodulation (including tDCS) in healthy individuals and a number of patient populations including stroke and will serve as a mentor for the project, providing tDCS training and will assist in reviewing MRI scans.

Name	Affiliation	Role
Mo Chen, PhD	University Minnesota Twin Cities	Consultant

Dr. Chen is a postdoctoral associate in the Program in Physical Therapy and Rehabilitation Science. As a biomedical engineer, he is able to provide custom equipment modifications and programming.

Name	Affiliation	Role
TBA	University of Wisconsin-River Falls	Research Assistant

A first year graduate student from the Department of Communicative Disorders will be selected as a research assistant based on GPA, clinical performance and experience with patients with aphasia. The research assistant will provide behavioral naming therapy (naïve to the treatment conditions) to the subjects under the supervision of the PI to avoid clinician bias in judging subject responses.

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