

Clinical Feasibility of Combining Transcranial Direct Current Stimulation with Standard Aphasia Therapy

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Abstract

Background: Transcranial direct current stimulation (tDCS) is a safe, portable, and inexpensive form of noninvasive brain stimulation that appears to augment the effects of concurrent therapy. However, several methodological issues in existing studies distance tDCS from current clinical practice. In this study, we offered (and administered) tDCS to individuals seeking typical behavioral aphasia therapy on an outpatient basis. **Methods:** We approached clients ($n = 10$) planning to receive standard aphasia therapy at a university clinic. Following a brief description of tDCS, we offered to provide stimulation during their therapy. Those interested and without contraindications participated in a double-blind, sham-controlled crossover study of tDCS paired with speech-language therapy provided twice weekly. Participants received active (2 mA) or sham tDCS during two eight-week therapy phases (separated by ten weeks) with the anode over Broca's area and the cathode on the contralateral forehead. Stimulation was provided for the first 20 minutes of each one-hour session. Prior to and following each phase, participants were video recorded telling the Cinderella narrative. Recordings were transcribed and analyzed for correct information units (CIUs). **Results:** Seven individuals (70%) were interested in and eligible for tDCS. Data from four participants who completed the study indicated a large effect size favoring active over sham tDCS (Cohen's $d = 1.32$). The participant with the most severe deficits did not benefit from therapy in either condition. **Conclusion:** There is potential for tDCS to enhance meaningful communication outcomes in standard clinical practice. Further investigation is needed to replicate findings and determine individual characteristics predictive of treatment response.

Keywords: Aphasia, rehabilitation, speech therapy, stroke, transcranial direct current stimulation

Guest editor's notes: While many studies have been published on pairing tDCS with aphasia therapy, none of them have paired tDCS with 'standard aphasia therapy' on a typical (non-intensive; i.e. 2x/week) therapy schedule. This fact is crucial for translation. It is true that an under-powered study like this one may fail to recognize a real difference between conditions. Hence, the fact that authors found a large effect size between active and sham stimulation, despite the small sample, might suggest that a larger sample would further support the current study's suggestions.

INTRODUCTION

Stroke is a leading cause of disability, with over 100 million survivors worldwide.^[1] Extrapolating from the literature on chronic stroke suggests 15 million or more of these individuals have persistent aphasia,^[2] a debilitating impairment that results in language deficits and diminished community integration and quality of life.^[3] In addition to the social, emotional, and vocational toll that aphasia exacts on individuals and families, this widespread condition economically burdens the health and social care systems that yet fail to meet consumer needs.^[4]

While aphasia has no cure, the standard treatment is speech-language therapy, typically targeting decreased impairment or increased ability to functionally compensate. Systematic review of the literature strongly supports the consistent but modest benefit of these behavioral interventions,^[5] suggesting the need to incorporate new approaches to reduce disability and improve quality of life. The potential benefit of a neuromodulatory treatment, transcranial direct current stimulation (tDCS), was first reported in 2007 as a serendipitous finding when four individuals with aphasia unexpectedly

showed improved language during a pilot study of tDCS targeting upper extremity functioning following stroke.^[6]

In tDCS, one electrode is affixed to the scalp, while at least one additional electrode is placed to complete the circuit, typically on the scalp or forehead, and a weak electrical current (≤ 4 milliamps; mA) is passed between them. In a manner reciprocal to how electroencephalography (EEG) records weak electrical signals through summation across

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coordinated neural ensembles, so too can tDCS exert effects on brain function, through minuscule electrical influences across large populations of neurons.^[7] Each electrode produces either a positive (anode) or negative (cathode) current, causing the affected neurons to experience subtle positive (excitatory) or negative (inhibitory) shifts in membrane potential that make action potentials respectively more or less likely to occur. While still in experimental stages and lacking high-quality evidence of benefit,^[8] initial studies of tDCS in aphasia support the utility of further investigation (e.g.,^[9]). As tDCS is safe, portable, and relatively inexpensive,^[10] it offers particular promise for direct translation into clinical applications. Further, while the precise mechanisms of its effect remain poorly understood, tDCS preferentially modulates brain networks that are engaged while the individual is receiving stimulation by potentiating existing neural activity.^[11] Thus, despite the need for further investigation, tDCS appears well suited to complement behavioral aphasia therapy.

To our knowledge, tDCS has not yet been combined with a “standard” aphasia therapy dose (i.e., routine clinical services provided outside of experimental laboratory paradigms). Although the theoretical basis and burgeoning evidence suggest that tDCS may be able to enhance the speed and extent of aphasia recovery when combined with appropriate therapy activities, several methodological issues in existing studies may distance tDCS from potential clinical translation. One issue is that it is unclear whether the general population of individuals with aphasia would be receptive to brain stimulation. It is plausible that individuals who volunteer for clinical trials and experimental treatments might represent a distinct subclass within that population, willing to engage in and tolerate a seemingly riskier intervention than those seeking standard speech-language therapy alone. A second issue is that many studies use either structural or functional neuroimaging to inform electrode placement on an individual basis, and this information is not typically available to a practicing speech therapist (except perhaps in gross anatomical terms from medical reports). A third issue is that studies pairing tDCS with aphasia therapy typically employ a more intensive schedule (five sessions weekly) than what is standardly provided, at least in the US, as outpatient treatment (two sessions weekly). To achieve this intensity (and for standardization), computer-based interventions are often employed, rather than personalized therapy with a skilled professional. Finally, existing studies have primarily focused on naming, rather than more functionally oriented therapies or outcome measures.^[12]

To address the issues outlined above, our starting point was to employ standard methods and dosing for behavioral aphasia therapy and then superimpose stimulation within this treatment context. Rather than actively recruiting for a clinical trial, we solicited study participants from a population seeking standard aphasia therapy, and then paired a uniform tDCS montage with this usual care. We also used a discourse measure, the number of correct information units (CIUs) produced during a narrative, as our outcome measure. In particular, we sought

to explore the following three issues related to the clinical feasibility of tDCS delivered in tandem with standard aphasia therapy:

1. Receptiveness: Are individuals seeking traditional behavioral therapy for aphasia interested in (and eligible for) tDCS as a treatment adjuvant?
2. Tolerability: Will individuals seeking traditional behavioral therapy for aphasia find the repeated application of tDCS acceptable for the duration of the therapy interval?
3. Efficacy: Does active tDCS paired with aphasia therapy, using a standard electrode montage and therapy dose, increase CIU production compared to placebo (sham stimulation)? If so, what sample size would be needed to demonstrate this difference statistically?

METHODS

Participants

We recruited individuals with chronic poststroke aphasia at a university clinic where they were scheduled to begin speech-language therapy. The inclusion criteria were ages 18–85 years; clinical diagnosis of aphasia; single left-hemisphere stroke ≥ 6 months prior to enrollment (confirmed by medical history and MRI); ability to participate in therapy tasks and provide written informed consent. The exclusion criteria were tDCS contraindications (e.g., pacemaker, epilepsy) and serious medical, neurological, or psychiatric conditions besides stroke comorbidities.

Seven individuals with aphasia were eligible and consented to participate in the study. Of these seven, two did not complete the study due to personal factors, unrelated to the research, that caused them to discontinue therapy. One further individual was excluded due to investigator error (technical issues and data loss). Therefore, complete data are presented for four individuals. All participants were monolingual English speakers and were premorbidly right-handed per self-report. The study was approved by the Institutional Review Board of Louisiana State University and written informed consent was obtained in accordance with the Declaration of Helsinki. This study was registered on ClinicalTrials.gov (Identifier: NCT03272906) prior to enrollment of the first participant. Enrollment was by invitation only due to our interest in restricting the study population to individuals seeking standard behavioral aphasia therapy at the clinic.

Study design

We employed a double-blind, sham-controlled crossover design. For inclusion, each participant was required to complete both an interval of active tDCS and an interval of sham tDCS (placebo) paired with aphasia therapy. Sham stimulation is described below. Each stimulation interval coincided with a semester in the university clinic schedule (fall or spring) and lasted 8 weeks; these intervals were separated by a period of 10 weeks. Stimulation order was randomized across participants. All personnel were blinded to stimulation

conditions until the completion and scoring of all assessment procedures following both stimulation intervals.

Outcomes assessment

Assessments were completed immediately prior to and following each stimulation interval. The primary outcome measure for this study was the production of correct information units (CIUs) during the telling of the narrative of Cinderella, a well-known fairy tale. Participants were first given a series of pictures (without text) depicting the sequence of events in the story to refamiliarize them with the tale. Following this review (self-terminated), the pictures were removed and participants were instructed to tell the story, with video recording for offline transcription and analysis. CIUs were calculated according to Nicholas & Brookshire guidelines.^[13] Briefly, words were counted as CIUs if they were intelligible, novel (i.e., not repeated), and appropriate to context.

For reliability, two trained research assistants transcribed each narrative using the Systematic Analysis of Language Transcripts (SALT) software.^[14] Transcription disagreements were resolved by the second author, who reviewed the original videos and then coded the transcripts for CIUs. Two additional research assistants were trained on CIU coding using a subset of the transcripts and then independently coded a different subset of transcripts (25%). Coding disagreements were resolved through discussion among the research assistants and both authors.

Therapy

Therapy was provided by student clinicians enrolled in a graduate training program in speech-language pathology under the supervision of a clinical faculty member with state licensure and US certification. Participants were scheduled for two 1-hour sessions weekly. Therapy goals were developed on the basis of each individual participant's needs and preferences, as determined by the treating clinician and clinical supervisor, without consideration of the research paradigm. Up to two sessions per stimulation interval were conducted as group therapy sessions. The decision to not constrain or dictate treatment goals or procedures was based on a desire to maximize ecological validity (i.e., closely approximate real-world therapy conditions). For each session, tDCS electrodes were placed immediately preceding therapy, which was initiated when stimulation began.

Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation was delivered using a Neuroconn DC-Stimulator Plus via two 5 × 7 cm saline-soaked, sponge-covered rubber electrodes. For all participants and all sessions, the anode was applied over Broca's area (identified as the crossing point between T3-Fz and F7-Cz per the EEG 10-20 system), and the cathode was placed on the contralateral forehead (Fp2). Active stimulation was provided at a current intensity of 2 mA (current density = 0.057 mA/cm²) for the first 20 minutes of each session and was ramped up and down to full intensity over a 30-second period for participant comfort.

Sham stimulation was delivered with parameters identical to the active condition, but for only a 30-second duration. This was intended to give the sensory perception of active stimulation without neuromodulatory effects. For double-blinding, the tDCS operator entered a randomly assigned code that determined whether active or sham stimulation was administered. The tDCS operator was not involved in the participant's therapy beyond the application of electrodes and stimulation, nor were they present in the room during therapy.

Prior to the initial session, scalp measurements were taken to identify electrode placements. An individualized headset was constructed from Velcro straps to permit quick placement before each therapy session, with markings to indicate the juncture of straps and electrodes as well as anatomical landmarks (e.g., nasion, ears). This headset was removed following the stimulation period or worn for the duration of therapy, as preferred by the participant.

Analysis

Receptiveness

To determine tDCS receptiveness of those seeking standard behavioral therapy, we calculated the percentage of clinic attendees with aphasia who were (i) both interested in and eligible for participation, (ii) interested but not eligible, and (iii) eligible but not interested.

Tolerability

To determine the tolerability of tDCS to enrolled participants, we provided the option of forgoing stimulation at each session. Participants also completed a survey of sensations following each stimulation interval (i.e., fall or spring semester) to determine the perceived comfort of the stimulation and to assess the effectiveness of blinding.^[15] To rule out a placebo effect, we compared the number of times that the stimulation condition (active vs. sham) was accurately identified by a participant following a stimulation interval. We calculated statistical significance by using a binomial probability distribution for the number of accurate identifications given the number of total responses. As there were three response choices ("real", "placebo", and "I don't know"), we calculated the probability of a correct response as 0.33 under the null hypothesis. We then used Fisher's exact test to determine whether the individuals were more accurate in identifying stimulation condition in the active vs. sham condition.

Efficacy

In order to determine whether tDCS may offer added value when paired with standard therapy, we compared the outcomes following the active stimulation interval to those following sham. We calculated effect size using Cohen's *d* for changes in CIU production across both intervals. Cohen's *d* is defined as the difference between two means divided by the pooled standard deviation of both samples. As this was a feasibility study underpowered to detect true between-condition differences, we used this effect size measure to perform a

power analysis and calculate the sample size necessary to yield statistically significant results in future studies.^[16]

RESULTS

Receptiveness

Ten individuals with poststroke aphasia were scheduled to begin speech-language therapy at the university clinic during the course of this study. Of these individuals, seven (70%) were both interested in and eligible for tDCS and consented to participate in the study. Two individuals (20%) were interested in participating but were ineligible due to tDCS exclusion criteria (pacemakers). One individual (10%) was eligible but not interested, expressing concern about potential safety issues related to electrical stimulation.

Tolerability

Four participants [Table 1] have complete data included here. As described in Methods, factors resulting in attrition or exclusion of the other three eligible individuals who provided consent were unrelated to the intervention or its perceived tolerability.

Data regarding the perceptual experience of stimulation, including effectiveness of blinding, is included in Table 2 for all participants who completed one full stimulation interval (either active or sham). Of the four participants who completed both stimulation intervals, three opted to forgo tDCS on a single occasion; each of these coincided with a group therapy session. Participants opted to receive tDCS for all other therapy sessions. Thus, of the 131 total therapy sessions provided to enrolled participants, tDCS was accepted during 128 (97.7%). There were no adverse events.

Stimulation condition was accurately identified following three of the ten completed stimulation intervals (30%), which was not significant compared to accuracy expected by chance (33%; $p = 0.69$). There was no significant difference in accuracy following active vs. sham stimulation ($p = 0.50$).

Efficacy

Individual results for the four participants who completed both stimulation intervals are included in Table 1 and Figure 1. Participants produced an average of 35.75 (± 33.1) more CIUs following active tDCS compared to an average of 0.25 (± 18.9) more CIUs following sham tDCS. Cohen's d for these outcomes corresponds to a very large effect size ($d = 1.32$) favoring active over sham tDCS. Mean reliability between the independent raters for CIUs was $>85\%$.

Using these findings, and presuming a one-tailed t-test, we calculated that this within-subjects design would require at least 12 participants to yield statistically significant results given the typical values of $\alpha = 0.05$ and $\beta = 0.20$, while a higher powered study ($\beta = 0.05$) would require 19 participants. A between-subjects design, presuming equal allocation to active vs. sham conditions, would require 16 ($\beta = 0.20$) to 28 ($\beta = 0.05$) participants.

DISCUSSION

We conducted a double-blind, sham-controlled crossover study of tDCS paired with standard aphasia therapy provided for two 1-hour weekly sessions over an 8-week duration, consistent with a common outpatient rehabilitation schedule. Participants with chronic aphasia were recruited from a university clinic to determine the receptiveness and perceived tolerability of electrical stimulation for individuals seeking traditional behavioral intervention, rather than an experimental trial. We also assessed the efficacy of the intervention using production of a discourse measure, rather than the naming outcomes often used in studies of tDCS in aphasia. This is the first known aphasia study to have employed tDCS within a purely clinical framework.

Of the ten individuals approached to participate in the study, eight were eligible based on exclusion criteria, and seven of these were receptive and enrolled. This may suggest that the majority of individuals seeking speech-language

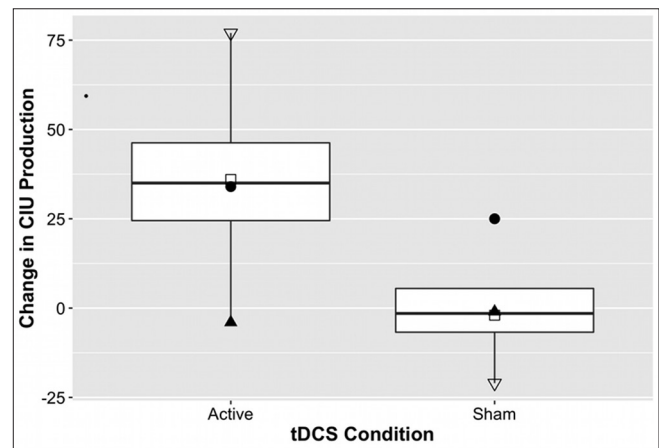


Figure 1: Boxplots for changes in correct information unit (CIU) production for active and sham stimulation intervals. Individual participants ($n = 4$) are represented by shape.

Table 1: Demographic and behavioral data for participants

Subject	Sex	Age	Education	Months Post Onset	Aphasia Type	WAB-AQ*	Change in CIUs†	
							Active	Sham
1	F	77	12	10	Broca's	43.7	-4	-1
2	F	55	16+	72	Anomic	89.4	+36	-2
3	F	82	14	14	Conduction	78.6	+77	-21
4	M	72	16+	50	Anomic	92.8	+34	+25

* Western Aphasia Battery Aphasia Quotient (maximum=100) at study baseline. †Change in correct information units produced during Cinderella narrative before vs. after active/sham stimulation

Table 2: Results of poststimulation sensation survey for active and sham conditions

	Active (n=4)	Sham (n=6)
Itching	Mild=1	
Pain		Mild=1
Burning	Mild=1	Mild=1 Strong=1
Warmth/Heat	Mild=1	Mild=1
Pinching	Mild=2	
Metallic/Iron Taste		
Fatigue	Mild=1	Mild=1
When did the discomfort begin?	At the beginning=3 At approximately the middle=1	At the beginning=4
How long did it last?	It stopped quickly=4	It stopped quickly=4
How much did these sensations affect your performance or focus?	Not at all=3 Slightly=1	Not at all=3 Slightly=1
Do you believe that you received real or placebo stimulation?	Real=2 Placebo=0 I don't know=2	Real=0 Placebo=1 I don't know=5

therapy to treat aphasia could be potential candidates for tDCS, in terms of both eligibility and interest. Pacemakers, currently a contraindication for electrical stimulation, made two potential participants ineligible, although preliminary research has demonstrated that tDCS does not affect pacemaker function.^[17] This suggests that such participants may ultimately be considered candidates for tDCS in the future. In this case, all participants approached would have been eligible for this intervention, and nine of ten (90%) would have been receptive to receiving stimulation, representing a compelling level of interest. All candidates were provided aphasia-friendly information on the experimental nature of the treatment and lack of current evidence of effectiveness. If beneficial tDCS effects were to become better established in the future, it seems reasonable to assume that patients' receptiveness might overall increase.

Regarding tolerability, participants accepted tDCS for all individual treatment sessions but did abstain for some (but not all) group sessions. Aphasia therapy is more typically provided in individual sessions; however, these observations may suggest that tDCS was perceived by participants as being either stigmatizing or cumbersome in a more "public" setting. This could be addressed socially through more widespread use of and familiarity with tDCS, cosmetically by concealing electrodes under (or integrating them into) a hat-type set up, or practically through use of smaller, more personal devices, which do exist but were not used in this study. This issue may bear further exploration if tDCS is empirically determined, in adequately powered studies, to be an effective treatment for aphasia, particularly if application is planned during group sessions or functional activities outside the clinic.

Qualitatively, perceived sensations were similar between active and sham tDCS. While participants were more likely to identify active stimulation as real and sham as placebo, these differences were not statistically significant. Participants generally reported being uncertain which type of stimulation they had received, despite the crossover design and even when active tDCS was received first. Reported discomfort was overall mild, occurring at the beginning of stimulation and stopping quickly, for both active stimulation and sham. The majority of participants did not find the stimulation to be distracting from therapy tasks, offering further support that tDCS could have strong potential for translational applications in the clinic. Our findings also support that the "ramp on-ramp off" method of blinding is adequate as a sham control at 2 mA, at least for this population.

The fundamental purpose of this study was to determine whether it might be possible to enhance functional communication benefits for people with aphasia through pairing of therapy with tDCS. Consistent with this hypothesis, we did find a significant increase in correct information units (CIUs) following intervals of active stimulation compared to sham, corresponding to a very large effect size for active tDCS (Cohen's $d = 1.32$). While clinicians treating aphasia do not typically assess discourse through the objective (but time-consuming) measures we propose, these measures are consistent with patient-centered therapy goals^[18] and, as such, might be used as criteria for self-termination of therapy. Our overall ideological approach was one of "backwards translation", in which research design decisions were made to ensure that techniques employed would be available to the intended end users (i.e., practicing clinicians and individuals with aphasia) by implementing methods connecting as tightly as possible to real-life situations.^[19] Thus, a key goal was to minimize the gap between laboratory implementation of tDCS and clinical practice standards for aphasia.

While it has been suggested that more intensive aphasia therapy may be more effective than the more commonly used spaced schedule applied here, these studies are typically confounded by the impact of overall dose.^[20] This is also the case for studies of tDCS, in which more stimulation sessions have been associated with more benefit, but attributed to intensity rather than overall quantity (e.g.,^[21]). If more intense dosing of aphasia therapy or tDCS is required to benefit patients, current therapy schedules and reimbursement protocols require re-examination. If less intense dosing, consistent with current spaced therapy schedules, may be equally (or more) effective, then emphasis should be placed on how these practices might be brought into the clinic to benefit patients in a manner as consistent with current practice as possible. Clearly, further exploration of these questions is required.

Here, we specifically focus on the effects of tDCS given a spaced therapy schedule, individualized treatment based on needs and preferences, and a functional outcome measure. Yet, tDCS represents only one form of transcranial electrical

stimulation (tES), which circumscribes a far larger parameter space. In addition to the need for comparative manipulations of design variables such as we consider, it should be emphasized that other aspects of tES remain underexplored, both in a general sense and in aphasia in particular. To begin, tDCS implies a constant current with (at least) one positive and one negative electrode. However, tES may also employ different waveforms, including alternating current, pulsed random noise, or any custom shape desired, which have received minimal attention in stroke or aphasia. In contrast, high-definition tDCS has previously been used in aphasia, (e.g.,^[22]) and this may ultimately prove more effective due to more focal targeting. Yet, it is also possible that some of the benefits observed for conventional (i.e., not high-definition) electrical stimulation in stroke may be due to an increased distribution of current through the highly conductive environment of cerebrospinal fluid, which could exert disproportionate (and beneficial) effects on perilesional regions theorized to be key in stroke recovery.

For tDCS, it remains unclear where electrodes should be placed or the intensity at which stimulation should be delivered. In this study, we selected electrode placement and intensity level based on previous studies that had demonstrated effect (e.g.,^[23]). As we were particularly interested in the potential for direct translation to the clinic, we employed a single, uniform electrode montage for all participants, naïve to lesion site. However, other studies have used magnetic resonance imaging (MRI) data about lesion location or activation foci to motivate electrode placement (e.g.,^[9]). The intensity at which stimulation should be delivered is also unclear, and it is notable that behavioral responses to current intensity do not scale linearly.^[24] Further, while most tDCS studies on aphasia provide anodal (putatively excitatory) stimulation to the lesioned hemisphere, effects have been found with cathodal (putatively inhibitory) stimulation on the lesioned side and contralesional anode placement.^[25]

All of these dosing variables likely interact and contribute their own critical effects, leaving an open question as to how tES may be optimized to most substantially benefit people with aphasia. In addition to the need for further behavioral studies, greater mechanistic understanding of how tES works, such as through explanatory use of neuroimaging to identify baseline characteristics and poststimulation network changes correlated with improved communication, may motivate new approaches and identify likely responders, whether to tES in general or to specific dosing parameters (i.e., personalized medicine). Anatomical or functional brain characteristics may be the key determinants when best practice guidelines are established. Regardless of whether this is ultimately found to be the case, such techniques will undoubtedly provide crucial information along the journey.

Limitations

The greatest limitation to this work is that it reports on an underpowered feasibility study with very small sample size. Additionally, there was extreme heterogeneity in terms of

baseline patient characteristics, aphasia type/severity, treating clinicians, sessions completed, and therapy goals/methods. The use of a uniform electrode montage, while practically motivated to maximize potential for clinical translation, may not be the best approach for all participants given the variability in lesion size and location; as with behavioral interventions, it seems unlikely that a “one size fits all” approach will ultimately prove the most effective. It is notable that one individual, who was the most severely impaired, did not demonstrate improvement following either active or sham stimulation, perhaps suggesting a critical threshold for residual language function for tDCS to be effective, or that an alternative stimulation approach (e.g., contralesional stimulation) is necessary for such cases. Given the pattern of study attrition, the three participants who did demonstrate improvement all received active tDCS first, despite planned counterbalancing. Finally, it is quite possible that the small sample in this study is not representative of most individuals seeking aphasia therapy, as the university clinic from which we recruited uses a private pay model. If our participants had previously exhausted their health insurance benefits for aphasia therapy, they may have been more motivated to try an experimental technique such as tDCS.

CONCLUSIONS

While it would be highly premature to extrapolate from the current findings, particularly given the very small sample size, they do suggest promise for the potential of tDCS to translate into standard clinical practice. Participants were both receptive to and tolerant of tDCS, and an increase in discourse production was demonstrated when biweekly therapy was paired with active, but not sham, stimulation. Future research is needed to determine whether these effects can be replicated in a larger sample. If noninvasive brain stimulation can enhance positive effects of behavioral intervention, incorporation into clinical practice could be radically beneficial for the millions of stroke survivors with aphasia.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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