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Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study

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Abstract

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by gradual deterioration of language function. We investigated whether two weeks of daily transcranial direct current stimulation (tDCS) treatment would improve language abilities in six people with a non-fluent form of PPA. tDCS was applied in an unblinded trial at an intensity of 1.5 mA for 20 min/day over 10 days. At the time of stimulation, patients were engaged in narrating one of several children's wordless picture stories. A battery of neuropsychological assessments was administered four times: at baseline, immediately following the 2-week stimulation period, and then 6-weeks and 12-weeks following the end of stimulation. We observed improvement in linguistic performance in the domains of speech production and grammatical comprehension. Our encouraging results indicate that larger, sham-controlled studies of tDCS as a potential intervention for PPA are warranted.

Keywords

Primary progressive aphasia; Logopenic PPA; Progressive nonfluent aphasia; tDCS; Neurodegenerative disease; Frontotemporal lobar degeneration

1. Introduction

1.1. Background

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by a gradual, irreversible decline of language function (Mesulam, 2001). Linguistic deficits vary between patients, impacting functions such as fluency of conversational speech, single word comprehension, repetition and naming ability. The condition is comprised of three clinical variants: nonfluent/agrammatic, semantic and logopenic. Nonfluent/agrammatic variant PPA

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(naPPA) is characterized primarily by slowed speech production with grammatical simplifications and errors, and is associated with atrophy of regions of the left frontal lobe (Grossman, 2012). Semantic variant PPA (svPPA) is associated with atrophy of the left anterior and ventral temporal lobe, and produces difficulty with naming and word comprehension that relates to broader deficits in semantic processing (Hodges & Patterson, 2007). Finally, logopenic variant PPA (lvPPA) is marked by atrophy of the left temporal and parietal lobes, which manifests as word-retrieval deficits and difficulty with repetition (Gorno-Tempini et al., 2008). Autopsy studies demonstrate that most patients with PPA have pathologic changes consistent with frontotemporal lobar degeneration (FTLD); however, Alzheimer's Disease (particularly in lvPPA) and other pathologies have also been associated with this syndrome (Grossman, 2010). There are no known treatments for PPA. The relentless progression of PPA symptoms eventually leads to a profound impairment in communication ability and, ultimately, to more generalized deficits of cognition.

1.2. Neuromodulation in PPA patients

While there is no cure for PPA, a few reports have suggested that some symptomatic improvement can be achieved through the use of behavioral (Henry et al., 2013; Louis et al., 2001) and neuromodulatory (Finocchiaro et al., 2006; Trebbastoni, Raccah, de Lena, Zangen, & Inghilleri, 2013) interventions. The two most widely used methods of noninvasive neuromodulation are Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). TMS is a form of noninvasive brain stimulation in which a magnetic coil is discharged over the skull to induce a brief current which depolarizes neuronal membranes, generating action potentials in neurons over the targeted area. Two small studies to date have explored whether TMS can be employed to facilitate language production in patients with PPA (Finocchiaro et al., 2006; Trebbastoni et al., 2013). Finocchiaro et al. (2006) found an improvement in verb production following five days of high-frequency (excitatory) rTMS to the left anterior midfrontal gyrus. In a more recent case study, Trebbastoni et al. (2013) demonstrated that five consecutive days of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) led to significant improvements in both oral and written language tasks.

In contrast to TMS, tDCS is a form of noninvasive brain stimulation in which small direct currents are applied through the skull in order to influence brain function (Nitsche & Paulus, 2000). Unlike TMS, tDCS does not generate action potentials, but rather may alter neuronal resting membrane potentials in order to increase (or decrease) the rate of cell firing in larger neural populations (Stagg & Nitsche, 2011). Compared to TMS, tDCS has a number of practical advantages including its ease of use, low cost, portability, ability to be paired with existing therapies, and outstanding safety profile (Poreisz, Boros, Antal, & Paulus, 2007). A number of studies have used tDCS for cognitive enhancement in domains such as working memory (Fregni et al., 2005; Gill, Shah-Basak, & Hamilton, 2014; Ohn et al., 2008) and language (Meinzer et al., 2014; Price, McAdams, Grossman, & Hamilton, 2015; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). It has also been extensively used for clinical applications in brain-injured patients (Baker, Rorden, & Fridriksson, 2010; Turkeltaub et al., 2012) as well as in patients with neurodegenerative disease (Benninger et

al., 2010; Boggio et al., 2011; Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008; Ferrucci et al., 2008; Hansen, 2012).

Recently there have been several reports in which tDCS was administered to people with PPA. These appeared to show significant improvement in some language functions in the absence of adverse effects (Cotelli et al., 2014; Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014; Wang, Wu, Chen, Yuan, & Zhang, 2013). A case study carried out by Wang et al. (2013) on a patient with naPPA demonstrated that five days of anodal tDCS over the left inferior frontal gyrus (IFG) and the left posterior peri-Sylvian region led to improvements in four subtests of the Psycholinguistic Assessment in Chinese Aphasia (PACA) battery. Recent work by Cotelli et al. (2014), also focusing on non-fluent patients, found improvements in naming abilities after two weeks of daily tDCS over the left DLPFC combined with concurrent language therapy in 8 patients. These improvements were sustained for up to 12 weeks after stimulation and, importantly, were not observed in the sham condition. Another recent trial by Tsapkini et al. (2014) demonstrated lasting improvements in word spelling following three weeks of daily tDCS over the left IFG combined with concurrent spelling intervention in 6 patients. Those patients that received active tDCS, as opposed to sham, were better able to spell words on which they were not trained, and these improvements were sustained for two months after stimulation. While these studies are encouraging, they have been limited in terms of the range of language abilities being investigated. Furthermore, the electrode montages employed were chosen for specific linguistic measures, and may not be effective for treating impairments in other language domains. Finally, previous studies have targeted patients with moderate to high disease severity, but it is unclear if tDCS will be effective in patients with relatively recent onset of symptoms. The current pilot study was designed to address these gaps in the literature.

1.3. Current study

In this proof-of-principle pilot study, we sought preliminary evidence to support the efficacy and tolerability of tDCS on PPA patients. We were interested in investigating the potential of tDCS to improve a wide range of language skills, insofar as prior studies have focused on a relatively restricted set of linguistic abilities, such as spelling (Tsapkini et al., 2014) and naming (Cotelli et al., 2014). To that end, in contrast to prior studies in which targets of stimulation were more spatially circumscribed, our tDCS montage was specifically chosen to maximize current distribution over a broad network of left-hemisphere language areas. As a result, we predicted improvement in a variety of linguistic abilities associated with the diagnostic features of the patients in our sample: these included speech production, repetition, grammatical comprehension and semantic processing. Finally, we also predicted that after repeated sessions of tDCS, these improvements would be sustained for several months beyond the initial stimulation period.

2. Methods

2.1. Participants

Patients with a diagnosis of PPA who had slowed speech were recruited from a large cohort of research participants at the Frontotemporal Degeneration Center at the University of

Pennsylvania. All participants had also been evaluated previously by a behavioral neurologist at the University of Pennsylvania and had been clinically diagnosed with a variant of PPA. Patients who scored below 15 on the mini-mental state exam (MMSE) were excluded due to concerns that global cognitive impairment might preclude their ability to follow directions and interfere with task performance. Potential participants were also excluded if they were non-native English speakers, or had a history of seizures or unexplained loss of consciousness, pregnancy, surgical breach of the skull, or any other medical or surgical contraindication to receiving noninvasive brain stimulation.

A total of 6 participants were recruited for this pilot study. Four of the patients had a diagnosis of lvPPA; the other two were diagnosed with naPPA, according to published criteria (Gorno-Tempini et al., 2011) and confirmation at a local consensus conference. lvPPA patients have lexical retrieval difficulty and repetition deficits; naPPA patients have slowed, effortful speech with deficits in grammatical expression, and a pattern of speech errors known as apraxia of speech. All participants thus displayed notable impairment in speech fluency. The average age was 66.2 ± 5.7 years and the average disease duration was 4.2 ± 1.8 years (see Table 1 for demographic information of the participants at baseline). The study was approved by the Institutional Review Board at the University of Pennsylvania and each patient provided informed consent to participate.

2.2. Design

This was an unblinded pilot study. All patients received two weeks (10 days) of active stimulation. During each 20-min stimulation session, patients narrated wordless children's picture books (see Section 2.4). Neuropsychological evaluation was administered at baseline (T0) and then immediately following the last tDCS session (T1). Follow-up assessments were performed at 6 weeks (T2) and 12 weeks (T3) ± 1 week following T1, and consisted of the same linguistic evaluation that was administered at baseline (see Fig. 1 for an overview of the study design).

2.3. Outcome measures

A battery of linguistic assessments was administered to each participant by a single tester (FG) trained in the administration of psychometric instruments. Depending on the individual, this battery took from 1 to 2 h to complete and was digitally audio-recorded for off-line analysis. The tests were administered in the same order for each person since the number of participants was insufficient to adequately counterbalance the order of testing. The linguistic assessment battery was designed to evaluate a wide range of language abilities corresponding to the symptom profiles of our participants. Included in the assessment were the following tasks: (1) Boston Naming Test (BNT): a commonly used measure of picture naming/word retrieval in which a line drawing is presented and participants are asked to name the object depicted (Kaplan, Goodglass, & Weintraub, 1983). Performance was measured by naming accuracy out of a subset of 15 items from the BNT. (2) Pyramids and Palm Trees (PPT): a standardized semantic categorization test in which participants see three words on a page and are asked to indicate which two "go together" (Howard & Patterson, 1992). Performance was scored by categorization accuracy on 26 word-triads. (3) Test for the Reception of Grammar (L-TROG): a standardized test in which people are asked to

match an orally presented sentence to one of two pictures (Charles et al., 2014). Accuracy was measured by correct identification of the target picture in 36 trials. (4) Category Naming Fluency: a series of tasks in which people are asked to generate as many words as possible in 1 min that are members of a specific category; semantic categories include animals, vegetables and tools (Carew, Lamar, Cloud, Grossman, & Libon, 1997). The total number of correct words counted for each category was then summed together to get a total. (5) Sentence Repetition was assessed using the materials developed by the NACC-FTLD consortium (Weintraub et al., 2009); participants were asked to repeat a series of sentences controlled for variables known to influence performance such as length, parts of speech, and imageability. Sentence Repetition was scored by counting the total number of completely correct sentences in 5 trials. (6) Elicited Speech Production: a semi-structured speech sample was elicited by presenting a black-and-white line drawing, the Cookie Theft picture from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983). Participants were asked to speak for 90 s, giving a description of the scene. The audio recordings of the Cookie Theft task were transcribed off-line by a blinded rater. The outcome measures were speech rate in words per minute (WPM), and mean length of utterance (MLU).

Two versions of this language battery were created (A and B), which contained different items on a subset of the tasks (BNT, PPT, and L-TROG), and were matched for difficulty between the two versions. Since these three tasks are all standardized and normed to allow for shorter versions (e.g., Mack, Freed, Williams, & Henderson, 1992), they were given in shortened forms in order to split up the trials between versions A and B. The two versions were administered in such a way that participants never received the same version in two consecutive testing sessions (e.g., ABAB or BABA). Two of the participants started with version A at baseline, while the other three started with version B.

We grouped our tasks into domain-based composite measures for the purposes of data analysis and interpretation. This allowed us to assess performance on clinically-relevant language domains which corresponded to the clinical features of PPA. The following domains were used: Speech Production, Repetition, Grammatical Comprehension and Semantic Processing. Speech Production was comprised of the speech rate and MLU measures from the Cookie Theft task. Though many tasks in the battery required the ability to produce speech, these two measures in particular relied primarily on grammatical expression, phonological awareness and verbal fluency – key aspects of speech production that were impaired in our sample. The Repetition domain consisted solely of the Sentence Repetition task. It was important to include this measure because repetition deficits are a core criterion for lvPPA (Gorno-Tempini et al., 2008). The Grammatical Comprehension domain was included because comprehension deficits (especially with longer sentences) are common in all variants of PPA; this domain was comprised solely of the L-TROG task. Finally, the Semantic Processing domain was comprised of the BNT, PPT and Category Naming Fluency tasks. Each of these tasks involves semantic memory and lexical retrieval, which are key components of semantic processing. Though BNT and Category Naming Fluency also have a verbal component, these tasks rely more heavily on semantics rather than speech production.

2.4. Transcranial direct current stimulation

tDCS was administered using a battery-driven, constant current Magstim Eldith system with 5 × 5 cm saline-soaked pads secured by a rubber strap. The current intensity was 1.5 mA (current density = 0.06 mA/cm^2) and the stimulation duration was 20 min, with a 30-s ramping period at the onset and at conclusion of stimulation. The anode was placed over the left fronto-temporal region of the brain (F7 in the International EEG 10–20 system (Homan, Herman, & Purdy, 1987)) and the cathode was placed over the left occipito-parietal region (O1). We modeled this montage using Soterix tDCS-Explore™ software and found that the current is well distributed throughout the language network in the left brain hemisphere (see Fig. 2).

There is evidence that engaging people in cognitive tasks that call upon the brain regions and networks that one wishes to enhance with tDCS results in selective modulation of those networks by stimulation (Gill et al., 2014). Based on this notion, patients were shown a wordless children's book such as *Frog, Where Are You?* (Mayer, 1969) during each 20-min period of stimulation (for a total of 200 min over two weeks) and asked to narrate the story. A different book was used each day and participants were engaged in narration for the duration of each tDCS session.

2.5. Statistics

Performance scores for each outcome measure were converted to z-scores based on the mean and standard deviation of each measure across all time points (T0, T1, T2 and T3). This was done for all 7 outcome measures. We grouped the tasks into composite measures that are relevant to the clinical features of PPA, as outlined in Section 2.3, and created domain scores based on aggregate z-score data of the respective tasks. These z-score composite measures allowed us to compare performance between tasks with differing scales, and also to track changes in clinically-relevant features of PPA.

Repeated measures ANOVAs were used to evaluate change in performance across the four time points used in the study (T0, T1, T2, T3). Separate ANOVAs were carried out for each of the composite domains, with performance at the four time points as within-subjects factors. Owing to our interest in each outcome measure as an indicator of clinically relevant and dissociable language ability and owing to our desire to avoid excessive type II error in this exploratory study, we did not employ correction for multiple comparisons in this analysis (see Rothman, 1990 and Perneger, 1998 for similar perspectives).

3. Results

3.1. Overall performance change

Repeated measures ANOVAs showed a significant change in performance across time points for 2 out of the 4 composite measures – Speech Production ($F(3,15) = 6.243$, $p = 0.006$) and Grammatical Comprehension ($F(3,15) = 8.391$, $p = 0.002$). There was no significant effect for the Repetition composite, $F(3,15) = 1.139$, $p = 0.365$, or for the Semantic Processing composite, $F(3,15) = 2.452$, $p = 0.103$, although scores for these measures did generally increase from baseline (see Table 2). In each analysis, Mauchly's Test of Sphericity

demonstrated that the sphericity assumption for parametric statistical tests had not been violated for each domain as well as the average across all domains (all *p*-values >0.05).

3.2. Performance change for each domain

Post hoc tests on the two statistically significant domains were carried out to investigate performance change from baseline at each of the time points. On Speech Production, there was significant improvement from T0 to T1 (−0.25 ± 1.02 vs. 0.23 ± 1.03, $p < 0.001$) and a trending improvement from T0 to T3 (−0.25 ± 1.02 vs. 0.002 ± 0.99, $p = 0.084$). On Grammatical Comprehension, there was significant improvement from T0 to T1 (−0.52 ± 1.15 vs. 0.14 ± 0.97, $p = 0.015$), from T0 to T2 (−0.52 ± 1.15 vs. 0.04 ± 1.03, $p = 0.002$), and from T0 to T3 (−0.52 ± 1.15 vs. 0.34 ± 0.88, $p = 0.010$). Finally, we averaged together the performance data from all four of the composites in order to get a measure of "global performance change" and ran a repeated measures ANOVA as in the previous analyses. The result for this Global measure was significant ($F(3,15) = 16.797$, $p < 0.001$) and showed improvement from T0 (−0.37 ± 0.63) to each of the subsequent time points: T1 (0.14 ± 0.45, $p = 0.010$), T2 (0.02 ± 0.52, $p = 0.012$), and T3 (0.21 ± 0.62, $p = 0.001$). Inspection of performance profiles for each participant indicated that each individual improved in their global measure of performance over time. Overall, after stimulation, patients showed improved performance from baseline on 2 out of the 4 tested domains, and demonstrated a sustained improvement in global performance on all 7 outcome measures (see Fig. 3 for graphs of key results).

4. Discussion

4.1. Summary and interpretation of results

In this unblinded pilot study involving six patients, we observed significant improvements on a variety of linguistic measures that were sustained for at least 3 months following tDCS. The current study builds upon and extends prior investigations of tDCS in patients with PPA in four important ways. Firstly, it greatly expands the range of language abilities being studied, examining not only picture naming ability but also speech fluency, grammatical comprehension, semantic processing and sentence repetition. Secondly, we employed an electrode montage that we believed would increase current flow to a broadly distributed network of left hemisphere peri-Sylvian areas in order to target this wide range of language abilities. Thirdly, our cohort was composed of a mix of patients with both lvPPA and naPPA. Though our modest sample size precluded a thorough analysis of each group separately, it is encouraging that we observed positive effects in all patients. Finally, the patients in our cohort had relatively mild disease progression and severity. Though it is unclear when best to administer tDCS for PPA, our results suggest that early treatment may be beneficial.

While prior studies involving tDCS in patients with PPA (e.g., Cotelli et al., 2014) demonstrated improvements in picture naming following tDCS, ours is the first to demonstrate improvements on key language functions of elicited speech production. We found that patients treated with tDCS displayed increased speech rate and utterance length in a spontaneous picture narration task. This is particularly significant because the participants in this study were recruited due to their slowed speech rate. Another novel effect that we

observed was improvement in grammatical comprehension. While we did not find significant effects in the other tested domains, we did find significant and sustained improvement in global performance on all the outcome measures. It is important to recognize that the typical trend for patients with PPA is for their language performance to deteriorate steadily over time (Libon et al., 2009; Mesulam, 2001; Xie et al., 2010). However, it appears that tDCS may ameliorate and in some cases reverse certain aspects of this decline, at least for three months following 10 days of stimulation. Within the context of a neurodegenerative syndrome like PPA, this preliminary finding is remarkable and merits further investigation with larger controlled studies.

Because our cohort was comprised of patients with the logopenic (N = 4) and non-fluent/agrammatic (N = 2) variants of PPA, we sought to assess performance in the specific domains associated with these clinical variants. One key feature associated with lvPPA is slow and effortful speech. This is due primarily to deficits in word-retrieval and phonological short-term memory; by contrast, in naPPA, this is due to difficulty integrating words within a grammatical framework (Gunawardena et al., 2010). These deficits can cause significant struggle with naming, repetition, speech fluency, and comprehension of long or complex sentences. Patients with naPPA have grammatical comprehension difficulty (Charles et al., 2014), and this too improved following stimulation. Though performance in sentence repetition and semantic processing did improve from baseline, our results were not statistically significant. This could be due to the high variance in performance, which likely stemmed from the difficult nature of the repetition task. In order for a sentence to be marked as correct on this task it had to be 100% correct. It appears that some of the patients struggled with this task, especially on the longer sentences. On the other hand, the tasks comprising the Semantic Processing domain may have been too easy, as the mean scores were very high and several of the participants displayed ceiling effects at baseline – especially on the BNT and PPT tasks. Moreover, semantic difficulties are not common in lvPPA and naPPA patients, especially for those with mild disease severity (Gorno-Tempini et al., 2011). Encouragingly though, our patients improved on speech rate and MLU in a semi-structured speech sample (Cookie Theft) and also on another task requiring timed language production (Category Naming Fluency). Overall, it seems that tDCS combined with a speech elicitation task for two weeks improved clinically-relevant features for up to three months in our mixed patient cohort.

4.2. Limitations

One limitation of our study is the lack of a sham stimulation control condition. Without such a control condition, it is difficult to say with certainty that the effects we observed were due to brain stimulation rather than other nonspecific factors, such as two weeks of daily sessions with a study coordinator and/or multiple exposures to the psychometric tests during follow-up. Although we cannot rule out practice or placebo effects without an appropriate sham condition, there is evidence that the measures we employed have good test-retest reliability (Flanagan & Jackson, 1997; Strauss, Sherman, & Spreen, 2006). As a result, we would not expect performance on these measures to vary significantly between testing sessions due to factors such as motivation or rapport. It is also unlikely that practice on the outcome measures alone can explain improved performance since PPA patients seen at the

Frontotemporal Degeneration Center have not improved in the past with many more weeks of traditional speech therapy. Furthermore, by administering two alternating versions of the language battery and by not correcting participants on their erroneous responses, we sought to minimize practice effects on the task stimuli, at least for the BNT, PPT and L-TROG. It is unlikely that practice effects would be elicited from the Cookie Theft or Sentence Repetition measures since these tasks rely more on productive capacity rather than executive components. The only remaining task for which practice effects may be a concern is Category Naming Fluency. However, there is evidence that these effects are small in healthy individuals, and are not found at all in patients with dementia, even when they are tested multiple times in the same week (Cooper et al., 2001).

Another limitation of this study is the small sample size and the fact that our cohort was skewed toward female patients with the logopenic variant of PPA. While it is known that females can exhibit a lesser degree of language lateralization compared to males (Clements et al., 2006), there is no current evidence to suggest that tDCS of the dominant hemisphere would work differently in females with PPA compared to males. It is also possible that other variants of PPA (e.g., svPPA) may respond differently to the specific tDCS parameters we employed. For both gender and PPA subtype, it is reassuring that we were able to replicate findings from other studies that had used a more equal distribution. Both of these limitations would be addressed by future trials that involve larger patient samples.

One other concern is that, although we did not include any language training in our study, it is possible that the picture book narration task performed during the two weeks of tDCS may have served as a kind of language intervention. We think this is unlikely because there is little evidence that PPA patients demonstrate sustained improvement in their speech expression or comprehension with such limited behavioral speech therapy (but see the results of more extensive exposure in Croot, Nickels, Laurence, & Manning, 2009). However, it is important to view the experience of our PPA patients in the context of their degenerative disease. For people with PPA it is highly unlikely that either rehearsal of the picture book narration task or prior exposure to the language measures of the study would have resulted in broad improvement in performance of multiple language tests that persisted for three months.

5. Conclusion

In light of the unrelenting language decline typically observed in patients with PPA, the results of this proof-of-principle study are very promising. Our finding that tDCS paired with a speech elicitation task induced persistent improvement in language skills in patients affected by this debilitating chronic progressive neurodegenerative condition clearly warrants further investigation. Moreover, our preliminary results suggest that our approach of broad left hemisphere language network stimulation may be appropriate for addressing the array of language deficits seen in patients with PPA and may also have promising implications for other domain-specific neurocognitive degenerative conditions. Future studies should examine these and other language measures in more depth with the goal of establishing the preferred stimulation montages needed to target these linguistic domains.

Finally, an investigation of the optimal time course of tDCS treatment should be carried out in order to test our preliminary finding of the benefit of early intervention.

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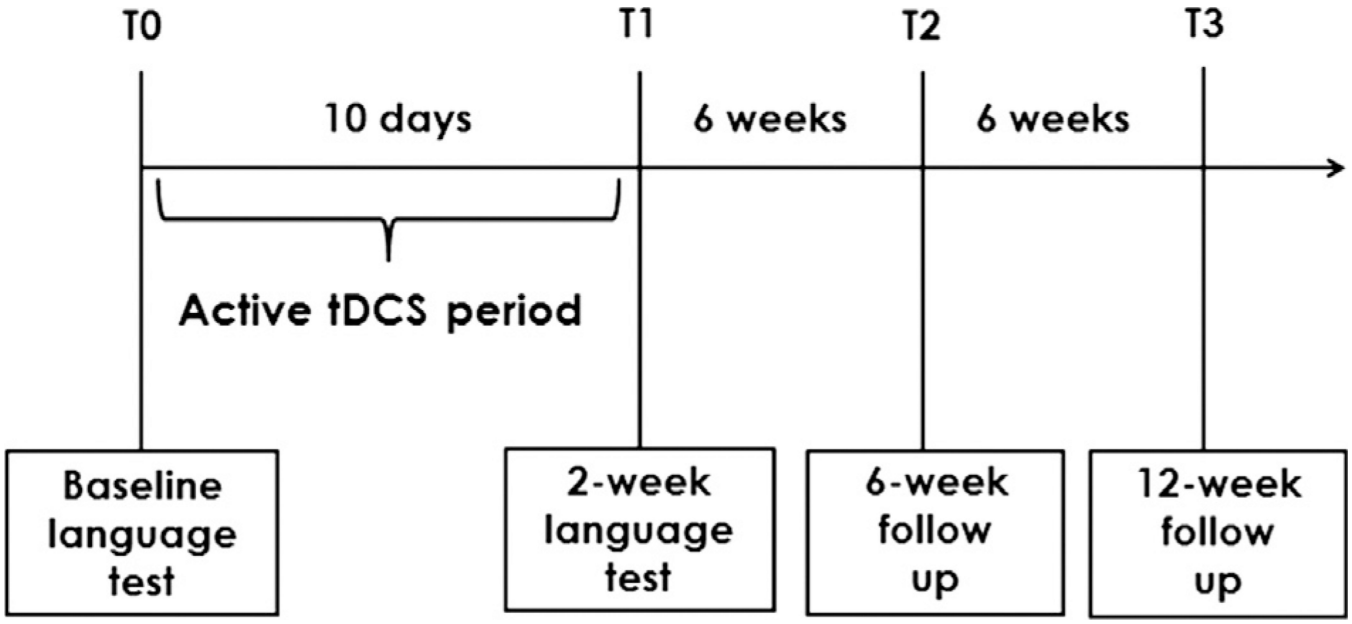

Fig. 1.

Study design. A language evaluation was conducted at each time point (T0–T3). The active stimulation period took place over two weeks (Monday through Friday).

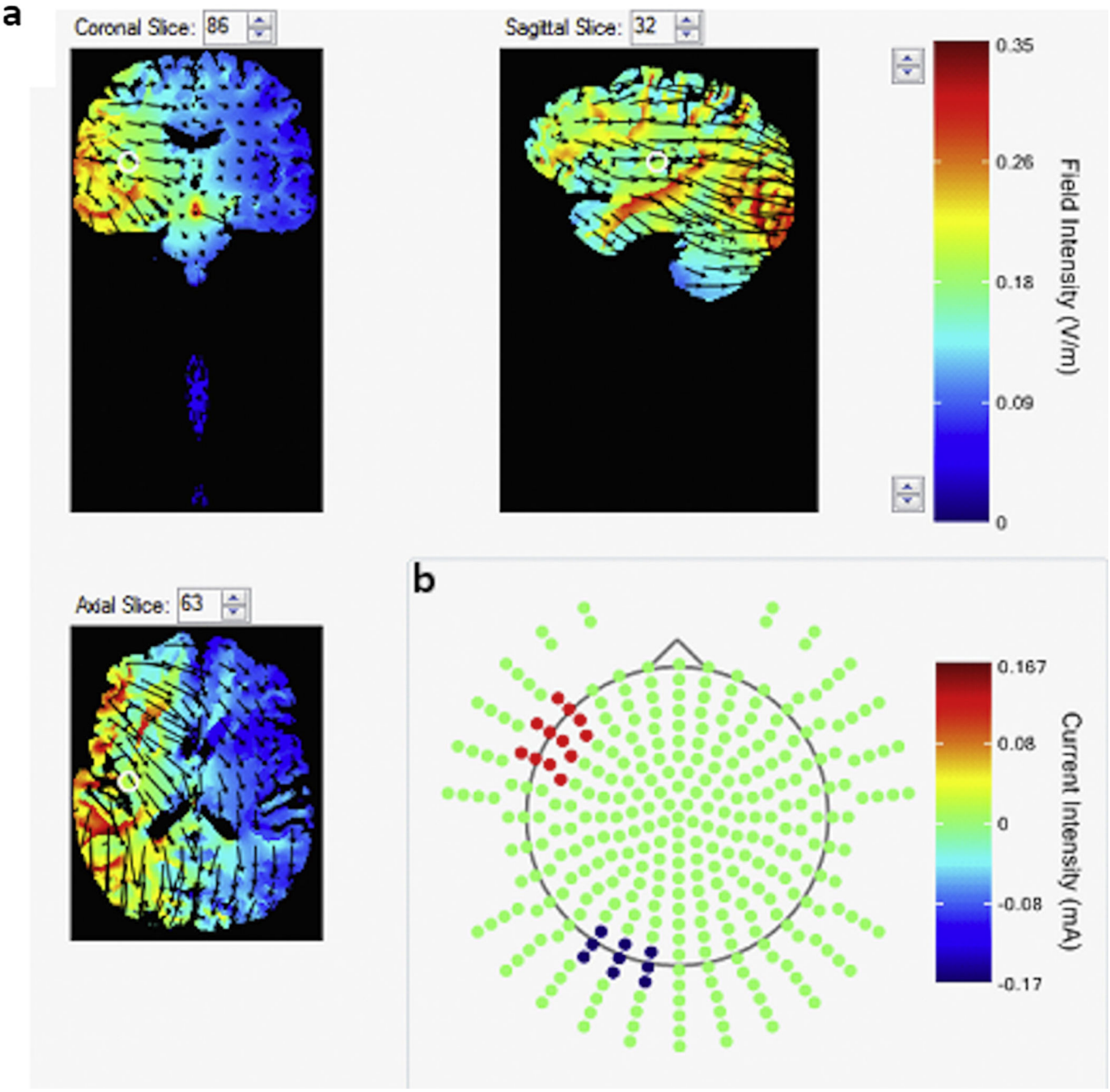

Fig. 2.

tDCS parameters. (a) Modeling of tDCS montage using Soterix tDCS-Explore™ software. (b) Electrode montage. Anode was over F7 (red) and cathode was over O1 (blue).

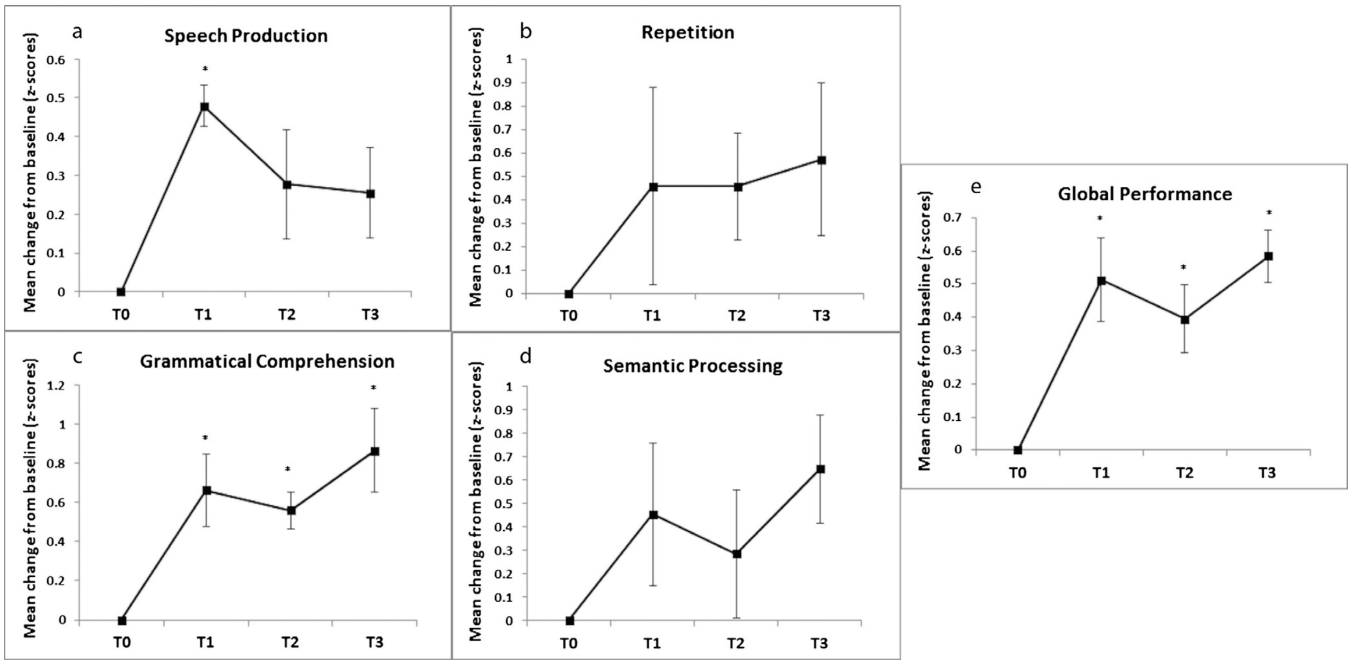

Fig. 3.

Change in performance of study participants from baseline (T0) to 2 weeks (T1), and 6 (T2) and 12 (T3) weeks after stimulation on (a) Speech Production, (b) Repetition, (c) Grammatical Comprehension, (d) Semantic Processing, and (e) Global Performance. (*$p < 0.05$). Error bars represent standard error of the mean.

Table 1

Demographic characteristics of study participants. Age, disease duration, and MMSE score were all determined at the beginning of participation.

Number of males/females	1/5
Age (yrs)	66.2 ± 5.7
Education (yrs)	16.3 ± 2.7
MMSE score	28.2 ± 1.2
Diagnosis (lvPPA/naPPA)	4/2
Disease duration at baseline (yrs)	4.2 ± 1.8

Table 2

Data table showing results on all outcome measures for study participants.

Domain	Outcome measure	T0 score Mean ± SD	T1 score Mean ± SD	T2 score Mean ± SD	T3 score Mean ± SD
Speech Production	*Cookie Theft*				
	Words per minute	74.5 ± 47.0	88.8 ± 40.3	84.8 ± 45.4	77.7 ± 38.0
	Mean length of utterance	9.3 ± 2.7	11.1 ± 3.2	10.2 ± 3.4	10.6 ± 3.2
Grammatical Comprehension	*L-TROG*				
	Accuracy (max = 36)	30.9 ± 3.8	33.0 ± 3.2	32.7 ± 3.4	33.5 ± 3.2
Repetition	*Sentence Repetition*				
	Accuracy (max = 5)	2.2 ± 1.3	2.8 ± 1.7	2.8 ± 1.2	3.0 ± 1.8
Semantic Processing	*Boston Naming Test*				
	Accuracy (max = 15)	13.2 ± 1.4	13.9 ± 1.0	13.9 ± 1.2	14.2 ± 1.0
	Pyramids and Palm Trees				
	Accuracy (max = 26)	24.9 ± 1.6	25.5 ± 0.6	24.7 ± 1.8	25.7 ± 0.5
	Category Naming Fluency				
	Total	28.5 ± 11.1	31.3 ± 14.0	33.5 ± 14.2	33.2 ± 14.5