Title
Cerebellar neuromodulation improves naming in post-stroke aphasia

Running Title
Cerebellar neuromodulation in aphasia

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Abstract

Transcranial direct current stimulation has been shown to increase the efficiency of language therapy in chronic aphasia; however, to date, an optimal stimulation site has not been identified. We investigated whether neuromodulation of the right cerebellum can improve naming skills in chronic aphasia. Using a randomized, double-blind, sham-controlled, within-subject crossover study design, participants received anodal cerebellar stimulation (n=12) or cathodal cerebellar stimulation (n=12) + computerized aphasia therapy then sham + computerized aphasia therapy, or the opposite order. There was no significant effect of treatment (cerebellar stimulation vs sham) for trained naming. However, there was a significant order x treatment interaction, indicating that cerebellar stimulation was more effective than sham immediately post-treatment for participants who received cerebellar stimulation in the first phase. There was a significant effect of treatment (cerebellar stimulation vs sham) for untrained naming immediately post-treatment and the significant improvement in untrained naming was maintained at two months post-treatment. Greater gains in naming (relative to sham) were noted for participants receiving cathodal stimulation for both trained and untrained items. Thus, our study provides evidence that repetitive cerebellar transcranial direct stimulation combined with computerized aphasia treatment can improve picture naming in chronic post-stroke aphasia. These findings suggest that the right cerebellum might be an optimal stimulation site for aphasia rehabilitation and this could be an answer to handle heterogeneous participants who vary in their size and site of left hemisphere lesions.

Key words:
cerebellum, aphasia, language therapy, stroke, transcranial direct current stimulation

Abbreviations

tDCS=transcranial direct current stimulation; BDAE=Boston Diagnostic Aphasia Examination; PNT=Philadelphia Naming Test; mA=milliamps

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Introduction

Anomia, or difficulty with naming, is the most common deficit in individuals with post-stroke aphasia, adversely impacting daily functioning and quality of life (Hilari et al., 2012). Transcranial direct current stimulation (tDCS) is a promising treatment modality that has been shown to increase the efficiency of anomia treatment in post-stroke aphasia (for reviews see Holland and Crinion, 2012; de Aguiar et al., 2015; Sandars et al., 2016; Bucur and Papagno, 2019; Elsner et al., 2019; Breining and Sebastian, 2020). A majority of the previous tDCS studies focusing on anomia treatment have targeted the intact perilesional left hemisphere regions. With respect to the stimulation locations, studies have targeted the left dorsolateral prefrontal cortex (e.g., Pestalozzi et al., 2018), left inferior frontal gyrus (e.g., Campana et al., 2015; Spielmann et al., 2018), left motor cortex (e.g., Meinzer et al., 2016; Darkow et al., 2017), left posterior perisylvian region (Wu et al., 2015), individualized optimal stimulation location using behavioral experiments prior to treatment (Shah-Basak et al., 2015), or individualized stimulation location on the basis of pre-treatment functional MRI (Baker et al., 2010; Fridriksson et al., 2011, 2018, 2019).

Individualizing stimulation location based on functional MRI can lead to substantial gains in language performance over that of treatment alone (sham) as demonstrated in a large randomized clinical trial (Fridriksson et al., 2018, 2019); however, it is cost-intensive and requires substantial technological expertise, thereby limiting the incorporation of tDCS in therapy clinics. Encephalomalacia at the lesion site also makes directly targeting the perilesional cortex difficult. Shunting of electrical current through the area of encephalomalacia may also result in unpredictable effects that vary from person to person (Turkeltaub et al., 2016). Targeting right hemisphere language homologs is an alternative approach, although the role of the right
hemisphere in aphasia recovery is still hotly debated. It remains unclear whether excitation or inhibition is the preferred strategy for the right hemisphere neuromodulation (Anglade et al., 2014, Gainotti, 2015).

The right cerebellum could potentially be an optimal site for tDCS treatment in post-stroke aphasia. Multiple lines of evidence suggest that the right cerebellum is involved in a variety of cognitive and language functions, including word retrieval and generation, verbal working memory, language learning, and semantic processing (for reviews see Desmond and Fiez, 1998; Murdoch, 2010; Stoodley, 2012; Keren-Happuch et al., 2014; Marien et al., 2014; Marien, 2017). The right cerebellum is distant enough from typical stroke locations associated with aphasia that electrical current flow patterns are unlikely to be affected by the encephalomalacia. Our group did a modeling study to understand the electric field distribution of the right cerebellar tDCS (Sebastian et al., 2017). The results indicated that the maximum electric field amplitude was generated in the right cerebellum with some spread to the left cerebellum but without spread to the adjacent occipital cortex or other cortical regions. Therefore, the right cerebellum might provide a structurally intact gateway to the affected neural networks of the cerebrum (Wessel and Hummel, 2018). Wessel and Hummel, 2018 argue that cerebellar stimulation could be an answer to handle the heterogeneous features of stroke. By targeting the cerebellum, the same protocol can be used in different patient populations, leading to better patient stratification.

Cerebellar tDCS studies in healthy individuals provide evidence that tDCS to the right cerebellum can modulate language functions. Pope and Miall, 2012 reported that right cerebellar cathodal tDCS improved performance on a verb generation task relative to anodal and sham tDCS. Turkeltaub et al., 2016 showed that both anodal and cathodal cerebellar tDCS improved verbal fluency performance, with a more robust effect for anodal tDCS. In addition, Turkeltaub and
colleagues show that cerebellar tDCS can modulate connectivity between the right cerebellum and the left hemisphere language regions (Turkeltaub et al., 2016 D’Mello et al., 2017).

With respect to post-stroke aphasia and cerebellar tDCS, a case study by Sebastian et al., 2017 showed that both anodal cerebellar tDCS and sham tDCS coupled with language treatment resulted in improved spelling to dictation for trained and untrained words immediately after and 2 months post-treatment. However, the improvement was greater with anodal tDCS than with sham, especially for untrained items. Further, generalization to written picture naming was noted only with tDCS. In another study, Marangolo and colleagues (Marangolo et al., 2018) investigated the effect of cerebellar tDCS coupled with language treatment in improving performance in a verb generation task in patients with aphasia. They used a randomized, double-blind, crossover study design. Each participant received cerebellar tDCS in four experimental conditions (right cathodal and sham stimulations during verb generation and verb naming tasks). Significant improvement was found only in the verb generation task following cathodal stimulation. The authors hypothesized that cerebellar tDCS is a viable tool for recovery from aphasia, particularly when the language task also demands the activation of nonlinguistic strategies, as in the case of the verb generation task, which requires executive and memory components.

Based on promising results of cerebellar tDCS in improving language skills in healthy controls and stroke participants with aphasia, we investigated whether tDCS to the right cerebellum coupled with computerized aphasia treatment can improve naming performance in individuals with chronic aphasia. Additionally, we investigated whether there are any differences in anodal vs cathodal cerebellar tDCS on naming performance as prior studies have shown beneficial language effects for anodal and cathodal cerebellar stimulation (Pope & Miall, 2012, Turkeltaub et al., 2016; Sebastian et al., 2017, Marangolo et al., 2018).
Materials and Methods

Study Design

A randomized, double-blind, sham-controlled, within-subject crossover study design was utilized. Participants who met eligibility criteria were randomly assigned using block randomization with a ratio of 1:1 to group anode or group cathode. Within each group, participants were randomly assigned to receive either ‘tDCS (tDCS first) then sham (sham second)’ or ‘sham (sham first) then tDCS (tDCS second)”. We used a crossover design to facilitate recruitment and reduce the effects of individual variability. The order of real and sham stimulation sessions was counterbalanced across participants.

Participants

Twenty-four right-handed participants with chronic aphasia participated in our study. Participant recruitment flowchart is depicted in Supplementary Figure 1. This study is part of a larger study examining the behavioral and neural correlates of cerebellar tDCS in aphasia treatment [Clinical Trial registration NCT02901574]. Participants’ demographic information is summarized in Table 1. Most participants had large left middle cerebral artery strokes. Participant inclusion criteria were: left hemisphere stroke; longer than 6 months post-stroke; previously right-handed; aphasia as confirmed by using the short version of the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 2001); and able to achieve at least 65% accuracy on a screening version of the aphasia treatment task (see details in the section titled Aphasia Treatment). Exclusion criteria were: lesion in the right cerebellum; a history of brain surgery; seizures during the previous 12 months; sensitive scalp (per patient report); and greater than 80% naming accuracy on the Philadelphia Naming Test (PNT; Roach et al., 2006). All participants provided written informed
consent prior to participating in the study. The study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine, where all data collection occurred.

[Insert Table 1 about here]

**Procedure**

The initial screening visit occurred over 2 days. Participants underwent a detailed medical history, neurologic examination, and language assessment using the following tests: BDAE-short form (Goodglass *et al.*, 2001), Boston Naming Test–short version (Mack *et al.*, 1992), Pyramids and Palm Trees-short Version (Breining *et al.*, 2015a), Hopkins Action Naming Test (Breining *et al.*, 2015b), and PNT (Roach *et al.*, 2006). Supplementary Table 1 shows language test scores for participants. Participants also completed an MRI session, which included T1- and T2-weighted structural MRI scan to rule out a lesion in the right cerebellum (stimulation site). For participants with contraindication for MRI (e.g., pace maker, claustrophobia, ferromagnetic implants), we used their previously available MRI/CT scan. Participants took part in 2 intervention phases of 15 treatment sessions (3-5 sessions per week) with tDCS + computerized aphasia therapy and sham + computerized aphasia therapy, or the opposite order. Each intervention phase was separated by a washout period of 2 months. Before the start of phase 1 treatment, each participant received language assessments including outcome variables (T1, pre-treatment, phase 1). The same assessments were carried out at the end of 15 treatment sessions of either real or sham tDCS (T2, post-treatment, phase 1) and at 2 months post-treatment (T3, 2 months post-treatment, phase 1). The T3 assessment also served as a second baseline assessment (T1, pre-treatment, phase 2) for participants as they crossed over into the next phase of the study. After the second baseline assessment, participants began the second round of 15 treatment sessions of either real or sham tDCS. If they had received real stimulation first, they crossed over into the sham condition; if they
received sham first, they crossed over into the real condition. Assessments were administered post-treatment (T2, post-treatment, phase 2), and at 2 months post-treatment (T3, 2 months post-treatment, phase 2) (Fig. 1A).

Transcranial Direct Current Stimulation

Brain stimulation was delivered for 20 minutes using a constant current stimulator (ActivaDose II tDCS Device or Soterix Medical 1x1 clinical trials device). Consistent with other studies on cerebellar tDCS (Ferrucci et al., 2016; Pope and Miall, 2012, Turkultaub et al., 2016, Sebastian et al., 2017), the current study utilized 2 milliamps (mA) of anodal tDCS or cathodal tDCS generated between two 5 cm x 5 cm saline soaked sponges. The active electrode (anode in ‘group anode’ or cathode in ‘group cathode’) was placed on the right cerebellar cortex, 1 cm under, and 4 cm lateral to the inion (approximately comparable to the projection of cerebellar lobule VII onto the scalp (Pope and Miall, 2012). The reference electrode (cathode in ‘group anode’ or anode in ‘group cathode’) was placed on the right shoulder (Fig. 1B).

Randomization and Blinding

All participants and all members of the study team who administered the assessments and treatments were blinded to the order in which the participants received tDCS and sham stimulations. To blind participants as to whether they were receiving real or sham tDCS, the same scalp sensation was induced during the start of the sham tDCS sessions, in which the tDCS stimulation was applied to the scalp for 30 seconds in a ramp up fashion, and then the current was gradually decreased over 15 seconds (Gandiga et al., 2006). Stimulation (for both conditions) started at the same time as the computerized aphasia treatment. Aphasia treatment continued for
another 25 minutes after the completion of 20 minutes of real tDCS or sham tDCS. For the Soterix device, blinding was achieved by inputting a 6-digit blinded code for initiation of stimulation. For the Activa Dose Device, blinding was achieved by a custom hardware device developed by Julius Fridriksson’s group (see Fridriksson et al., 2018 for details). This hardware device was attached to the tDCS device. New codes or hardware boxes were provided to the treating clinician for each patient prior to the start of each intervention period. The senior authors of the study (AEH and DCT) performed the randomization and blinding. Blinding integrity was assessed at the end of each treatment phase.

**Aphasia Treatment**

We utilized a treatment program developed by Julius Fridriksson and colleagues (Fridriksson et al., 2009, 2011, 2018). The aphasia treatment was performed through a computerized task that involved matching pictures depicting common objects with words that were heard and seen (the face of the speaker below the nose is shown on the computer screen). The treatment involves all aspects of lexical-semantic processing and has been shown to improve naming in stroke patients with different underlying causes of naming deficits (Fridriksson et al., 2009). The treatment program consisted of 160 color pictures depicting low-, medium-, and high-frequency nouns and was randomly presented four times during the treatment with a semantic foil, phonological foil, unrelated word, or target word. Half of the pairs represented a correct match. During treatment, a picture appeared on the computer screen for two to five seconds. Then, a video of the speaker was presented on the screen saying a word that either matched or did not match the preceding picture. The participant was instructed to press a green response button if the picture and spoken word matched and a red response button if they did not match. Immediate feedback was provided.
following each response in the form of a “smiley face” for correct responses and a “frowny face” for incorrect responses (Fig. 2). The computer program did not proceed to the next item until a response was recorded for the previous item. The duration of the stimulus presentation and time to respond was adjusted to match the speed of the participant. To ensure that participants with aphasia understand the treatment task, a pre-treatment screen, identical to the treatment task, was administered. Screening involved 40 high-frequency words: participants were given three chances to achieve 65% accuracy, a level of accuracy demonstrating that he or she understands the task requirements.

[Insert Figure 2 about here]

**Outcome Measures**

Two outcome measures were used in this study: change from baseline in number of the correctly named items on the Naming 80 Test (trained naming) and change from baseline in the number of correctly named items on the PNT (untrained naming). Naming 80 Test consists of a subset of 80 pictures utilized in the treatment program. It should be noted that the treatment program consisted of 160 pictures; however, only half of the treatment items were selected to decrease assessment time at each time. All outcome measures were assessed before and after the end of the treatment, and at two months post-treatment completion for the tDCS and sham conditions. Naming accuracy was scored based on PNT scoring guidelines (Roach *et al.*, 1996).

**Adverse Effects**

Participants were assessed at the end of each treatment session for pain and discomfort. We used the Wong-Baker FACES Pain Rating Scale (Wong and Baker, 1988) to assess pain associated with
tDCS. In addition, we also asked the participants if they had any discomforts such as itching, irritation, tingling, or burning at the end of each treatment session.

**Statistical Analysis**

Descriptive statistics and t-tests were used to compare participant characteristics and adverse effects. To assess the effect of tDCS treatment on change in naming accuracy, we performed separate linear mixed-effects models for the two outcome measures: Naming 80 test (trained naming) and PNT (untrained naming). Linear mixed-effects regression models with a random intercept for participants were fit via the maximum likelihood method using the MIXED command in Stata. Change in correct naming immediately post-treatment minus pre-treatment and two months post-treatment minus pre-treatment for the sham and tDCS conditions was the dependent variable. Fixed effects including the following: Treatment (two levels: tDCS vs sham), Time (two levels: 2 months post-treatment vs post-treatment), Order of treatment (two levels: tDCS first then sham vs the reverse), and their interactions. An additional model was fit separated by group (anode vs cathode). The main effects and interactions of the variables in the models were evaluated by the Wald tests. LINCOM command in Stata was used to estimate the difference between the coefficients of tDCS and sham conditions for significant main effects and their interactions. Statistical analyses were done with Stata, version 16 (Statacorp, College Station, TX).

**Data Availability**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.
Results

Of the 24 enrolled participants, 21 completed the study; 3 dropped out during phase 1 and were not considered in the present analyses. P16 dropped out because of personal reasons, and P6 and P11 dropped out due to an illness unrelated to the study.

Safety and Tolerability

All 21 participants tolerated the stimulation well without any adverse effects. With respect to pain, no participants reported pain during the tDCS stimulation sessions. One participant reported very mild pain (Wong and Baker pain rating scale score=1) during one of the sham sessions. For the other four symptoms (irritation, itching, burning or tingling sensation) we scored yes=1 or no=0 for each session. We compared irritation, itching, tingling and burning from 315 sessions for tDCS and sham conditions. Transient irritation was reported for 3% (SD= 0.18) of the tDCS sessions and 0.6% (SD=0.05) for the sham sessions; transient itching was reported for 5.7% (SD= 0.23) of the tDCS sessions and 4.7% (SD=0.21) for the sham sessions, tingling was not reported for any of the tDCS sessions and 0.6% (SD=0.05) was reported for the sham sessions, and burning was reported by 1 participant during one tDCS session. No significant differences were evident between the tDCS and sham sessions with the exception of ‘irritation’ which was more pronounced during tDCS \[t (314) =2.92, p=0.004].

Integrity of Blinding

To ensure proper blinding, each participant and clinician was asked to guess the stimulation type at the end of each treatment phase. Stroke participants’ guessing accuracy was 42.8% and the
The clinician’s guessing accuracy was 47.6%. This indicates that each group’s accuracy was essentially at chance.

**Participant Treatment Accuracy**

All participants improved on the aphasia treatment task as indicated by greater task accuracy on the last treatment session compared with the first treatment session. The mean change in accuracy between the last and the first treatment session was significant for both phase 1 and phase 2. Phase 1: mean change in accuracy= 12.93%, SD=8.7 [t (20) =6.63, p=0.000], phase 2: mean change in accuracy=7.67, SD=8.26 [t (20) =4.15, p=0.001].

**Outcome Variables**

At baseline before the start of phase 1 treatment, there was no statistically significant difference between the groups. Naming 80: Group Anode (M=10.60, SE=3.89) and group Cathode (M=15.64, SE=4.38), [t (19) = 0.85, p=0.40] and PNT: Group Anode (M=50.70 SE=15.05) and group Cathode (M=54.09, SE=12.67), [t (19) = 0.17, p=0.86]. In addition, there was no statistically significant difference between the groups for months post onset since stroke: Group Anode: M=27.40, SE=7.05) and group Cathode (M=34.81, SE=10.34), [t (19) = 0.58, p=0.56].

**Naming 80 Test (trained naming)**

In the initial model (combining both groups), there was no significant effect for treatment, time, or order. However, there was a significant order x treatment interaction immediately post-treatment (p=0.004). The interaction was such that for participants who received tDCS first (order: tDCS first then sham), there was a significant improvement in naming immediately post
tDCS compared to sham (difference in mean change in naming accuracy between tDCS and sham was 5.8, 95% CI from 1.5 to 10.1, p = 0.008) vs no significant improvement in naming immediately post tDCS compared to sham if sham came first (the difference in mean change in naming accuracy between tDCS and sham -2.9, 95% CI from -6.98 to 1.16, p = 0.16 for participants who received sham first). There was no statistically significant difference between tDCS and sham at the two months post-treatment for either order of treatment (b=-.9; 95% CI: -5.16 to 3.37; p = 0.68 if tDCS was received first and b=1.2; 95% CI: -2.96 to 5.44; p = 0.56 if sham was received first). Figure 3 shows the mean change from baseline in Naming 80 Test accuracy for tDCS and sham conditions. Supplementary Table 2 and Supplementary Figure 2 shows the mean Naming 80 Test accuracy separated by phase, condition, and time. Supplementary Figure 4 shows the individual data points across the three time points for Naming 80 Test.

[Insert Figure 3 about here]

In the second model (separated by group), there was no significant main effect for treatment, time, or order for group anode and group cathode. No interaction effects were significant for group anode. However, similar to the initial model, there was a significant order x treatment interaction for group cathode (p=0.022). The interaction was such that for participants in group cathode who received tDCS first (order: ‘tDCS first then sham’), there was a significant improvement in naming immediately post tDCS compared to sham (difference in mean change in naming accuracy for tDCS and sham was 6.8, 95% CI from 1.76 to 11.84, p-value = 0.008), vs no significant improvement in naming immediately post tDCS compared to sham if sham came first (the difference in mean change in naming accuracy between tDCS and sham -1.17, 95% CI from -5.77 to 3.44, p = 0.62 for participants who received ‘sham first’). The treatment effect at the two
months post-treatment did not reach statistical significance regardless of order: for participants who received tDCS first (b=3.0; 95% CI: −2.04 to 8.04; \(p = 0.24\)) or for participants who received sham first (b=2.3; 95% CI: −2.61 to 7.17; \(p = 0.36\)). Figure 4 shows the mean change in Naming 80 Test accuracy separated by group (anode, cathode) and order (‘tDCS first then sham’, ‘sham first then tDCS’).

[Insert Figure 4 about here]

**PNT (untrained naming)**

In the initial model (combining both groups), there was a significant effect of treatment (\(p=0.015\)). However, there were no statistically significant order or time interactions, which indicated that the effect for treatment did not significantly vary by time post-treatment or the order in which the treatment was received. For order ‘tDCS first then sham’, the mean difference in change in naming accuracy between tDCS and sham was 9.57 (95% CI from 1.7 to 17.38, \(p = 0.016\)) immediately post-treatment. Likewise, at 2 months post-treatment, the mean difference in change in naming accuracy between tDCS and sham was 10.22 (95% CI from 2.22 to 18.22, \(p = 0.012\)). For order ‘sham first then tDCS’, the mean difference in change in naming accuracy between tDCS and sham was 6.22 (95% CI from -.87 to 13.31, \(p = 0.086\)) immediately post-treatment. Similarly, at the 2 months post-treatment, the mean difference in change in naming accuracy between tDCS and sham was 11.39 (95% CI from 4.30 to 18.48, \(p = 0.002\)). No other interactions (2- or 3-way) reached significance. Figure 5 shows the mean change from baseline in PNT accuracy for tDCS and sham conditions. Supplementary Table 2 and Supplementary Figure 3 shows the mean PNT accuracy separated by phase, condition, and time. Supplementary Figure 5 shows the individual data points across the three time points for PNT.

[Insert Figure 5 about here]
In the second model (separated by group), no statistically significant treatment effects were observed in group anode. In the model for group cathode, similar to the combined models, treatment effects did not significantly vary by time point or order, i.e. no statistically significant interactions were observed. For group cathode, for order ‘tDCS first then sham’, the mean difference in change in naming accuracy between tDCS and sham was 15.24 (95% CI from 3.81 to 26.68, p = 0.009) immediately post-treatment and 15.25 (95% CI from 3.2 to 27.23, p = 0.013) 2 months post-treatment. For order ‘sham first then tDCS’, the mean difference in change in naming accuracy between tDCS and sham was 3.97 (95% CI from -5.48 to 13.43, p = 0.41) immediately post-treatment and 12.86 (95% CI from 3.39 to 22.32, p = 0.008) 2 months post-treatment. Figure 6 shows the mean change in PNT accuracy separated by group (anode, cathode) and order (tDCS first then sham, sham first then tDCS).

[Insert Figure 6 about here]

Discussion

Neuromodulation is a promising adjunct to speech and language treatment of post-stroke aphasia; however, to date, an optimal stimulation site has not been identified. In this study, we show that stimulation of the right posterolateral cerebellum combined with computerized aphasia treatment can improve picture naming in chronic post-stroke aphasia. There are three main results of this study: (1) for trained items, the effect for cerebellar tDCS was not significant. The order x treatment interaction was however significant, indicating that cerebellar tDCS was more effective than sham immediately post-treatment for participants who received stimulation in phase 1 (order ‘tDCS first’); (2) for untrained items, the effect of cerebellar tDCS was significant immediately
post-treatment and at two months post-treatment; and (3) greater gains in naming (relative to sham) were noted for participants receiving cathodal stimulation for both trained and untrained items.

**Potential Mechanism of Action of Cerebellar tDCS**

The increased behavioral gains observed for untrained and (less striking in) trained naming could be due to the relatively high duration and intensity of stimulation (15 sessions, 3–5 times per week of tDCS). At the cortical level, repeated tDCS sessions administered concurrently with behavioral training are thought to act via mechanisms similar to long-term potentiation, which is critical for neuroplasticity and memory consolidation (Reis *et al*., 2009, 2015; Fritsch *et al*., 2010). However, it’s unknown whether these mechanisms also underlie the improvement in behavior observed with cerebellar tDCS.

It has been proposed that cerebellar tDCS is most likely to produce its effects by polarizing Purkinje cells and changing the levels/pattern of activity in the deep cerebellar output nuclei (Galea *et al*., 2009; Grimaldi *et al*., 2016). Evidence from animal studies suggest that Purkinje cells respond to cerebellar tDCS (Grimaldi *et al*., 2016). Thus, it is likely that cerebellar tDCS could influence long-term depression (LTD) in Purkinje cells. LTD of Purkinje cells plays a role not only in motor function but also in cognitive tasks (Vigot, 2003). Animal studies have also shown that learning is mediated in part by LTD in Purkinje cells (Ito, 1982). Based on this, we speculate that the improvement observed in naming skills could be related to the role of the cerebellum in learning. Previous studies in humans have shown that cerebellar tDCS facilitates motor skill learning (Canterero *et al*., 2015, Wessel *et al*., 2016) and procedural learning (Ferucci *et al*., 2013). Cortical tDCS studies have reported beneficial effects of stimulation on language learning for familiar and unfamiliar objects (e.g., Meinzer *et al*., 2014; Fiori *et al*., 2018). In addition,
multisession cortical tDCS studies report transfer effects to untrained materials (Cappelletti et al., 2013, Park et al., 2014). Therefore, multisession cerebellar tDCS combined with aphasia treatment may enhance the learning of compensatory strategies and re-learning of language during aphasia treatment, resulting in improvement in trained and untrained naming.

**Polarity Independent Effect on Naming**

The performance of participants receiving cathodal stimulation (relative to sham) was better compared to participants receiving anodal stimulation (relative to sham) for order ‘tDCS first’ for both trained and untrained items. Significantly greater gains in naming was noted for group cathode immediately post-treatment and at 2 months post-treatment for order ‘tDCS first’. However, the overall mean changes in naming (combining both phases) were similar in group anode and group cathode immediately post-treatment. At 2 months post-treatment, the overall mean change in naming was higher for group cathode compared to group anode. Our results suggest that cathodal stimulation might be more favorable than anodal stimulation but the fairly small difference does not allow strong conclusions regarding polarity specific effects.

Thus, these findings are consistent with the as-yet unclear directionality of the effects of anodal vs cathodal cerebellar tDCS on cognitive task performance (Grimaldi et al., 2016). The results of the present study are not unusual since anodal and cathodal cerebellar tDCS have been reported to have polarity-independent effects on working memory (e.g., Ferucci et al., 2013), motor learning (e.g., Galea et al., 2009), and language processing (e.g., Pope and Miall, 2012). For example, in a study of verb generation in healthy individuals, cathodal cerebellar tDCS applied over the right cerebellum facilitated performance on the verb generation task, as compared to anodal tDCS and sham tDCS (Pope and Miall, 2012). In contrast, Turkeltaub et al., 2016 found
that both anodal and cathodal cerebellar tDCS enhanced the performance on a phonemic fluency task compared to sham; however, the anodal effect was found to be more robust.

The lack of polarity specific effects could be due to the complexity of gyral folding of the cerebellar cortex, which in turn can causes hyperpolarization in some neurons while others may be depolarized simultaneously, leading to different global effects of cerebellar tDCS (Woods et al., 2016; van Dun et al., 2016b). In addition, it is also unclear whether cerebellar tDCS affects only the Purkinje cells or whether it affects other entities, such as parallel fibers, climbing fibers, mossy fibers, and basket cells. Furthermore, substantial individual variability in anatomy as well as the neurophysiological constitution, plays a critical role in the efficacy of cerebellar tDCS (Oldrati and Schutter, 2018). Thus, the difference seen between group anode and group cathode could also be related to individual variability.

**Differential Effect of Cerebellar tDCS in the Crossover Phase**

An important finding was that tDCS effects compared to sham were more pronounced for order ‘tDCS first’ for both trained and untrained naming. Although, the order effect was not significant, the mean gain in naming was higher for order ‘tDCS first then sham’ compared to ‘sham first then tDCS’. One possible explanation for this finding could be related to the role that the cerebellum plays in language processing. Prior studies have shown that the role cerebellum plays in language processing depends on task demands (Stoodley et al., 2010, 2012; Pope and Miall, 2012, 2014; Boehringer et al., 2013; Marangolo et al., 2018). Both tDCS and sham conditions were paired with a computerized aphasia treatment task that involved matching pictures depicting common objects with words that were heard and seen. Color pictures depicting low-, medium-, and high-frequency nouns were randomly presented four times during the treatment with a semantic foil, phonological foil, unrelated word, or target word. Participants had to press two
different buttons to indicate whether the picture and spoken word matched or did not match. Participants also received immediate feedback on whether their response was correct or incorrect. Our working hypothesis is that the right cerebellum showed increased preferential activity during learning in phase 1, which then decreased as the task was repeated and became more efficient. It should be noted that even though participants showed a significant improvement on the aphasia treatment task (indicated by greater task accuracy on the last treatment session compared with the first treatment session) for both phase 1 and 2, the magnitude of improvement was lower in phase 2 compared to phase 1. Thus, lower tDCS treatment gains in phase 2 could be due to the treatment task becoming more automatic and easier to perform (with some participants being at or near ceiling at the beginning of phase 2).

Another explanation for lower treatment gains in phase 2 could be due to tDCS carry over effects. We took several steps to minimize the potential for carryover effects. We used a 2-month break in between phase 1 and phase 2 with the assumption that the tDCS effect will have washed out by that time. In addition, we also adopted an analysis approach utilized by our colleagues (Tsapkini et al., 2018; de Aguiar et al., 2020) to allow for the case that the tDCS effect does not wash out in 2 months. In our analysis, we used the ‘change in naming’ as the main outcome, i.e., the score at each post-treatment/follow-up minus the score at baseline of the respective phase. This means that any effect of tDCS vs sham found in phase 2 will not reflect the improvement itself at the level of performance in naming, i.e., the fact that the participants who got tDCS first are naming more accurately than those who got sham. Therefore, any effect of tDCS vs sham that carries over from 2 months of phase 1 to only the level of performance in phase 2 will cancel in the tDCS vs sham comparisons of ‘change in naming’ at phase 2. In this way, we eliminated one of the possible “carryover” effects of tDCS: the improvement at the mere level of performance (Tsapkini et al.,
Indeed, it is possible that tDCS effects carry over into the subsequent sham condition for some participants, resulting in an inflated sham performance in the second phase.

Individual Variability in Cerebellar tDCS Response

The results of this study indicate that there is marked individual variability in the cerebellar tDCS response. Based on the spaghetti plots shown in the supplementary Figures 4 and 5, it is evident that some participants showed large gains, some showed small gains, and some did not show any gains at all. In general, a majority of the participants showed improvement with tDCS despite severe aphasia; however, participants with profound naming deficits showed no change or very minimal change (participants with naming score of 0). It is possible that participants with some residual naming ability could derive greater benefit from combining cerebellar tDCS with training compared to participants who have profound naming deficits.

Cerebellar tDCS and Computerized Aphasia Treatment

The results of our study add to the growing number of studies that indicate that repetitive sessions of tDCS combined with language therapy can enhance the naming outcomes in chronic aphasia. However, closer inspection of the results of the published studies reveals substantial heterogeneity of the tDCS response. One reason could be that different types of therapy may have differential effects on the nature and extent of neuroplasticity that occurs within the language networks and may differentially engage left-hemisphere versus right-hemisphere networks (Crosson et al., 2019), resulting in a variable treatment outcome. One can reduce the treatment-induced variability by using a therapy protocol that has been successfully paired with tDCS. We utilized a computerized treatment task that has been shown to improve naming in participants with
aphasia when combined with tDCS (Baker et al., 2010; Fridriksson et al., 2011, 2018, 2019). Similar to the Fridriksson et al. 2018, 2019 studies, we found greater improvement in naming with tDCS compared to sham. However, there are several differences in study design: parallel sham-controlled study vs within-subject cross over study; left hemisphere anodal stimulation vs right cerebellar anodal/cathodal stimulation; 1mA vs 2mA current strength. Please see supplementary Table 3 for a comparison of Cohen's $d$'s between our study vs Fridriksson et al. 2018, 2019. We chose a computerized aphasia treatment program because the treatment time and intensity were the same for the tDCS and sham conditions. There are other types of aphasia treatments that are probably equally or more effective for improving naming; however, the purpose of the current study was not to evaluate the effectiveness of aphasia treatment but to determine the adjuvant benefit of cerebellar tDCS when combined with a proven form of computerized aphasia treatment.

**Limitations**

There are several limitations to our study. Our sample size is small; therefore, these findings need to be confirmed in a larger trial. A second limitation is that we assessed pain and discomfort at the end of each 45-minute treatment session. It is possible that any pain due to tDCS would have subsided by the time the pain scale was administered. However, due to the nature of the treatment task (computerized treatment task), it was not possible to administer the pain scale right after the completion of the stimulation at 20 minutes. A third limitation is that we cannot determine if improvement in naming translates to improvements in functional communication or quality of life for participants with aphasia. We are currently analyzing the ASHA FACS (American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults) scores in a subset of our participants to determine whether improvement in naming translates to
improvements in functional communication. A fourth limitation is that the individual variability observed in this study could be related to the medications the participants were taking. A recent review indicates that many medications may impact the efficacy of tDCS (McLaren et al., 2018). For example, selective serotonin reuptake inhibitors (SSRIs) have been shown to influence the after effects of tDCS (Nitsche et al., 2009). Seven participants in this study were taking SSRI. However, given this was a crossover study, and participants were likely taking the same medications in both phases, it is unclear to what extent medications (including SSRIs) might have interacted with tDCS to influence the results of the study. Finally, performance of participants receiving anodal was not significantly different from sham for trained and untrained items. This could be due to a small sample size and/or individual variability. Future investigations will need to address the polarity specific mechanism of action of cerebellar tDCS to refine its application in aphasia rehabilitation. Resting state functional connectivity might provide key insights into the neural mechanisms underlying polarity-specific changes in the network dynamics induced by cerebellar tDCS. Such imaging may aid in determining predictors of treatment outcome for anodal and cathodal tDCS, in order to provide more effective, targeted treatment for people with aphasia.

Conclusions

This study provides novel evidence that repeated stimulation of the right cerebellum along with aphasia treatment can improve naming in chronic post-stroke aphasia. Cerebellar tDCS is easily delivered, is well tolerated, and has not shown serious adverse effects. In addition, cerebellar tDCS montage can be easily implemented in clinical practice. Targeting the intact right cerebellum allows for the possibility of identifying a single target that can be used across groups of people with aphasia with varying lesion sites and size in the left hemisphere.
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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at Brain Communication online.
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Figure Legends

**Figure 1. Study Design and Stimulation.** (A) A randomized, double-blind, sham controlled, within-subject crossover study design was utilized. Participants took part in 2 intervention phases, separated by a wash out period of 2 months. (B) 2 mA of anodal or cathodal stimulation was generated between two 5 cm x 5 cm saline soaked sponges, where one active electrode (anode in ‘group anode’ or cathode in ‘group cathode’) was placed on the right cerebellum, and the reference electrode (cathode in ‘group anode’ or anode in ‘group cathode’) was placed on the right shoulder.

**Figure 2. Computerized treatment task.** During treatment, a picture appeared on the computer screen followed by a video of the speaker saying a word that either matched or did not match the preceding picture. The participant was instructed to press a green response button if the picture and spoken word matched and a red response button if they did not match. Immediate feedback was provided following each response in the form of a “smiley face” for correct responses and a “frowny face” for incorrect responses.

**Figure 3. Trained Naming Accuracy.** Mean change from baseline in Naming 80 test accuracy for sham and tDCS conditions immediately post treatment and 2 months post treatment. Error bars show standard errors.

**Figure 4. Trained Naming Accuracy separated by Group and Order.** Mean change from baseline in Naming 80 test accuracy for group Anode and group Cathode. Within each group, participants were assigned to receive ‘tDCS first then sham’ or ‘sham first then tDCS’. ‘Blue’ and ‘Green’ colors show participants who received tDCS first followed by sham. ‘Brown’ and ‘Orange’ colors show participants who received sham first followed by tDCS. Error bars show standard errors.

**Figure 5. Untrained Naming Accuracy.** Mean change from baseline in PNT accuracy for sham and tDCS conditions immediately post treatment and 2 months post treatment. Error bars show standard errors.

**Figure 6. Untrained Naming Accuracy separated by Group and Order.** Mean change from baseline in PNT accuracy for group Anode and group Cathode. Within each group, participants were assigned to receive ‘tDCS first then sham’ or ‘sham first then tDCS’. ‘Blue’ and ‘Green’ colors show participants who received tDCS first followed by sham. ‘Brown’ and ‘Orange’ colors show participants who received sham first followed by tDCS. Error bars show standard errors.
Table 1: Demographic and Phase 1 baseline language scores for participants with aphasia

| Patient ID | Group | Age (years) | Gender | Education (years) | TPS | Lesion Location | Stimulation Order | Pre-Treatment Screening Accuracy | BDAE Aphasia Severity | Baseline Naming 80 scores | Baseline PNT scores |
|------------|-------|-------------|--------|-------------------|-----|-----------------|-------------------|---------------------------------|----------------------|-----------------------------|---------------------|
| P1         | Anode | 53          | M      | 18                | 12  | Left temporal, parietal | Sham first        | 85                              | 3                   | 28                          | 132                 |
| P2         | Anode | 76          | M      | 16                | 6.5 | Left temporal, insula   | Sham first        | 68                              | 1                   | 0                           | 0                   |
| P3         | Anode | 47          | M      | 18                | 10  | Left frontal, temporal, parietal, subcortical | Sham first        | 90                              | 3                   | 13                          | 88                  |
| P4         | Anode | 67          | M      | 10                | 26.5| Left frontal, temporal, parietal, insula | Sham first        | 78                              | 2                   | 2                           | 15                  |
| P5         | Anode | 79          | M      | 18                | 17  | Left subcortical, basal ganglia | Sham first        | 70                              | 2                   | 0                           | 21                  |
| P6         | Anode | 68          | M      | 14                | 72  | Left frontal, temporal, parietal | Sham first        | 78                              | 2                   | 13                          | 31                  |
| P7         | Anode | 65          | M      | 18                | 25  | Left frontal, temporal, parietal, insula, basal ganglia | tDCS first       | 85                              | 3                   | 10                          | 60                  |
| P8         | Anode | 60          | M      | 14                | 27  | Left frontal, temporal, parietal | tDCS first       | 89                              | 2                   | 23                          | 101                 |
| P9         | Anode | 78          | F      | 16                | 44  | Left temporal, parietal and occipital | tDCS first       | 85                              | 2                   | 0                           | 2                   |
| P10        | Anode | 67          | M      | 13                | 23  | Left frontal, temporal, parietal | tDCS first       | 77.5                            | 2                   | 0                           | 8                   |
| P11        | Anode | 37          | F      | 16                | 41.5| Left frontal, temporal, parietal | tDCS first       | 94                              | 4                   | 46                          | 125                 |
| P12        | Anode | 58          | M      | 15                | 83  | Left frontal, temporal | tDCS first       | 91.6                            | 3                   | 30                          | 80                  |
| P13        | Cathode | 64        | M      | 16                | 11.5| Left Basal ganglia, insula | Sham first        | 78                              | 4                   | 40                          | 113                 |
| P14        | Cathode | 56        | M      | 14                | 7.5 | Left frontal, temporal, parietal | Sham first        | 87.5                            | 3                   | 24                          | 87                  |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| P15 | Cathode | 72 | M | 16 | 35 | Left frontal, parietal, subcortical | Sham first | 77.5 | 2 | 1 | 16 |
| P16 | Cathode | 44 | M | 16 | 26 | Left frontal, parietal | Sham first | 91 | 3 | 36 | 96 |
| P17 | Cathode | 74 | M | 16 | 6 | Left temporal, parietal, occipital | Sham first | 78 | 2 | 2 | 20 |
| P18 | Cathode | 69 | F | 12 | 24 | Left frontal, insula, subcortical | Sham first | 76 | 3 | 11 | 30 |
| P19 | Cathode | 59 | M | 13 | 118 | Left frontal, temporal, parietal, occipital | Sham first | 70 | 3 | 19 | 60 |
| P20 | Cathode | 50 | M | 18 | 63 | Left temporal, parietal, subcortical | tDCS first | 91 | 3 | 16 | 81 |
| P21 | Cathode | 67 | F | 23 | 12 | Left frontal, temporal, parietal | tDCS first | 68 | 1 | 0 | 0 |
| P22 | Cathode | 66 | M | 14 | 6 | Left frontal, parietal | tDCS first | 68 | 1 | 0 | 0 |
| P23 | Cathode | 65 | M | 17 | 53 | Left temporal, parietal, insula, basal ganglia | tDCS first | 66 | 4 | 38 | 102 |
| P24 | Cathode | 58 | M | 16 | 47 | Left frontal, temporal, parietal, occipital, insula | tDCS first | 81 | 3 | 21 | 86 |

TPS: Time post stroke onset in months; BDAE: Boston Diagnostic Aphasia Examination; Baseline Naming 80: Correct scores for Naming 80 Test (trained naming) prior to starting Phase 1 treatment; Baseline PNT: Philadelphia Naming Test-Correct scores for PNT (untrained naming) prior to starting Phase 1 treatment.
Figure 1. Study Design and Stimulation. (A) A randomized, double-blind, sham controlled, within-subject crossover study design was utilized. Participants took part in 2 intervention phases, separated by a wash out period of 2 months. (B) 2 mA of anodal or cathodal stimulation was generated between two 5 cm x 5 cm saline soaked sponges, where one active electrode (anode in 'group anode' or cathode in 'group cathode') was placed on the right cerebellum, and the reference electrode (cathode in 'group anode' or anode in 'group cathode') was placed on the right shoulder.
Figure 2. Computerized treatment task. During treatment, a picture appeared on the computer screen followed by a video of the speaker saying a word that either matched or did not match the preceding picture. The participant was instructed to press a green response button if the picture and spoken word matched and a red response button if they did not match. Immediate feedback was provided following each response in the form of a “smiley face” for correct responses and a “frowny face” for incorrect responses.
Using a randomized, double-blind, sham-controlled, within-subject crossover study design, Sebastian et al. investigated whether cerebellar transcranial direct current stimulation combined with computerized aphasia treatment can improve picture naming in chronic aphasia. Results indicate significant improvement in untrained naming and trained naming (only for participants who received stimulation first) compared to sham.