Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Investigation of the effect of Delayed Auditory Feedback and transcranial Direct Current Stimulation (DAF-tDCS) treatment for the enhancement of speech fluency in adults who stutter: a Randomized Controlled Trial

Narges Moein
Iran University of Medical Sciences https://orcid.org/0000-0002-5102-5385
Reyhane Mohamadi (mohamadi.r@iums.ac)
Iran University of Medical Sciences
Reza Rostami
University of Tehran
Michael Nitsche
Libniz research centre for working environment and human factors
Reza Zomorrodi
Temetry Centre for Trapeutic Brain Intervention, University of Toronto
Amir Ostadi
University of Waterloo
Abbasali Keshtkar
Tehran University of Medical Sciences

Research

Keywords: Delayed Auditory Feedback, Stuttering, trans-cranial Direct Current Stimulation, speech fluency, adults who stutter

Posted Date: November 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-29391/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background: With a population prevalence of one percent, stuttering is among the main speech pathology-related topics of research. Adults who stutter may benefit from transcranial direct current stimulation (tDCS) as an adjunctive intervention for enhancing speech fluency. In this study, Delayed Auditory Feedback (DAF) was combined with tDCS applied over the superior temporal gyrus. It was anticipated that the combined intervention cause improvements in speech fluency.

Methods: A randomized, double-blind, sham-controlled clinical trial was conducted to investigate the effectiveness of intervention in enhancing speech fluency. Fifty participants were randomly allocated to the intervention or control group. In the intervention group, participants received DAF combined with anodal tDCS, while the control group was exposed to sham tDCS simultaneously with DAF. Each subject participated in six intervention sessions. Speech fluency was assessed as the baseline, before intervention as well as immediately, one week and six weeks after intervention.

Results: In the intervention group, the percentage of stuttered syllables was significantly reduced immediately, one week and six weeks after the intervention, as compared with the control group. The scores of the Stuttering Severity Instrument, also showed a significant reduction in the intervention group compared with the control group. No significant difference was found in the Overall Assessment of the Speaker's Experience of Stuttering questionnaire scores between the two groups after intervention.

Conclusion: The results of this study propose anodal tDCS as an adjunctive method to increase speech fluency in stuttering for a prolonged time course after intervention, when combined with fluency therapy.

Trial registration: This trial was registered in ClinicalTrial.gov before recruiting the subjects. The registration number is NCT03990168 and the date of registration is June 18, 2019. https://clinicaltrials.gov/ct2/show/NCT03990168

Introduction

Background

With a population prevalence of one percent, stuttering has gained critical attention and is among the main speech pathology-related topics of research in academia in the past few years [1, 2]. Although the issue of stuttering has seen advances in terms of diagnosis and treatment, there still exist major limitations such as instability of treatment outcomes and lack of knowledge about therapeutic long-term results which need to be addressed [3]. As reported in the literature by some recently conducted research work, adults who stutter may benefit from non-invasive brain stimulation as an adjunctive intervention for enhancing the results of speech fluency treatment [4]. One of the available tools that has recently received considerable attention in this regard is transcranial direct current stimulation (tDCS). In this noninvasive brain stimulation technique, a weak constant current of 1-2 mA is applied through the scalp and results in alteration of cortical excitability and activity [5].

In recent years, studies have shown that tDCS enhances speech and language skills in patients with aphasia or apraxia [6-10]. Naming skills improved after applying tDCS in patients with chronic aphasia who had non-fluent speech [6, 9] and the performance of patients with apraxia improved with respect to oral production and language tasks [7, 8]. In these studies, the anodal electrodes were placed over the frontal cortex and frontotemporal areas (Broca's region) [6-9]. Recent studies have shown that tDCS increases speech fluency also in adults who stutter when applied during a fluency intervention [4, 11]. According to findings which show that the frontal cortex shows abnormalities in individuals who stutter [12], this potential target area for tDCS has been tackled in a recently conducted study [4]. Chesters, Watkins, and Mottonen investigated the effect of five sessions of anodal tDCS over the left inferior frontal gyrus during a speech fluency intervention on stuttering. They have reported a significant improvement of speech fluency in the treatment group who received anodal tDCS combined with the fluency intervention in comparison with a respective sham tDCS group. It was concluded that simultaneous usage of tDCS with fluency intervention can enhance speech fluency in stutterers.

One method which has been shown to be effective in enhancing speech fluency in individuals who stutter is Delayed Auditory Feedback (DAF). DAF enhances speech fluency by altered timing of auditory feedback [13]. As reported in a recent study, enhancement of speech fluency in individuals who undergo DAF is associated with increased activity of the primary and secondary auditory areas in the superior temporal gyrus [13]. These areas show bilateral underactivity in stutterers, compared to those without respective symptoms, as shown by functional neuroimaging methods [12]. There are few issues with using DAF. For example in order for the treatment to be effective the device must be worn for at all time. In addition, although DAF can decrease the frequency of dysfluencies, it does not totally eliminate stuttering [14, 15]. To overcome these limitations, and therefore, to enhance the efficacy of the treatment, one approach is to use adjunctive interventions. In this study, DAF, as a speech fluency intervention, was combined with tDCS applied over the superior temporal gyrus (electrode position T3 of the 10-20 international system). By considering the fact that with tDCS, cortical functions can undergo plasticity-like changes which can outlast the stimulation period, it was anticipated that intervention cause improvements in speech fluency and these consequences would be seen for a longer period after intervention [16].

In tDCS, electrical current flows between two or more electrodes, a negatively charged cathode and a positively charged anode, which are positioned at specified locations on the scalp. Applying this current causes subtle changes in the resting membrane potential of cortical neurons in the underlying brain tissue [5]. Specifically, with standard protocols, effects under the cathode (cathodal stimulation) lead to hyperpolarization of respective neuronal compartments and decrease in neuronal excitability, while effects under the anode (anodal stimulation) result in depolarization and therefore increase in excitability, at macroscopic levels [17]. Neuroplastic effects which depend on alterations of glutamatergic, and GABAergic activity, emerge some minutes after stimulation [18, 19]. Similar to the acute membrane polarization effects, anodal and cathodal tDCS result in excitability-enhancing and excitability-reducing plasticity, respectively [16, 20, 21].

As mentioned above, in a meta-analysis study, Brown et al. (2005) showed that the primary and secondary auditory areas were under-activated bilaterally in stutterers when they speak [12]. In another meta-analysis study, Budde et al. (2014) argued that underactivity in the left auditory cortex is associated with the stuttering "trait" (between-group contrasts of stutterers with controls), whereas right auditory cortical activity is correlated with moments of stuttering or stuttering "state" (within-group contrasts of dysfluency with induced fluency in stutterers) [22]. Based on these studies, we hypothesized that stimulation of left superior temporal gyrus supports brain activity associated with a fluent speech rather than stuttered habitual speaking pattern. Therefore this stimulation may be effective as an adjunctive method to fluency training via DAF to enhance speech therapy success in adults who stutter. In addition, in order to investigate the long-term outcomes, we assessed the outcomes six weeks after intervention. This hypothesis was systematically tested in the present project.

Specific objectives

The purpose of this study was to investigate the effect of adjunctive non-invasive brain stimulation on speech fluency in adult stutterers. In order to fulfill this goal, we recruited two groups of stuttering adult participants, i.e. a control group and an intervention group. In the control group, the participants received sham stimulation during DAF, whereas the participants in the intervention group received anodal tDCS simultaneously with DAF as a fluency intervention. We hypothesized that the fluency intervention combined with anodal tDCS over the left superior temporal gyrus would be more effective as compared to the sham tDCS control condition in enhancing speech fluency in stutterers.

Measures of speech fluency were collected at 5 time points: one week and immediately before intervention as well as immediately, one week and six weeks after the intervention. Outcome measures were compared between control and intervention groups across these time points. The primary outcome measure was the mean score of the percentage of stuttered syllables (SS %) [23]. According to this, the primary objective of this study was to compare the mean score of the SS % between the intervention and the control group at 5 assessment time points. We hypothesized that the mean score of SS% at the three post-intervention time points (immediately, one week and six weeks after the intervention) would be statistically different between the intervention and the control groups.

Besides, we had two secondary outcomes measures; (i) the mean score of Stuttering Severity Instrument-Fourth Edition (SSI-4) [24], (ii) the mean score of OASES questionnaire [25]. Thus, two secondary objectives were defined as:

- Comparison of the mean score of the SSI-4 between the intervention and the control groups at 5 assessment time points. We hypothesized that the score of the SSI-4 at the three post-intervention time points would be statistically different between the intervention and the control groups.

- Comparison of the means of OASES questionnaire score between the intervention and control groups at 5 assessment time points. We hypothesized that the score of the OASES at the three post-intervention

time points would be statistically different between the intervention and the control groups.

Methods

Trial design

A randomized, double-blind, sham-controlled clinical trial was conducted to investigate the effectiveness of anodal tDCS combined with DAF in enhancing speech fluency in adults who stutter. Fifty participants were randomly allocated to one of the groups. In the intervention group, participants received DAF combined with anodal tDCS, while the control group was exposed to sham tDCS simultaneously with DAF.

Participants

The study population consisted of adults with developmental stuttering. Since this study addressed adults with at least moderate levels of stuttering, a speech-language pathologist assessed the severity of stuttering in each subject to determine whether he/she could be enrolled. In order to assess stuttering severity, the SSI-4 questionnaire was used. Inclusion criteria included history of developmental stuttering, diagnosed with moderate to severe stuttering, right-handed, age 18 to 50 years (adult), native speaker of Farsi, and non-smoker. Exclusion criteria included stuttering accompanied by other speech or language disorders, having stuttering treatment within the month before intervention, hearing loss, history of neurological or psychiatric disorders, history of seizures, intake of any medication that affects brain functions, such as anti-depressants, pregnancy, breast-feeding, cranial bone defects, cranial/brain metal implants, and skin lesions. The CONSORT flow diagram for this study is shown in Figure 1.

Interventions

In this study, two pre-intervention assessments were performed for baseline measures. These were conducted one week and immediately before intervention. Once the assessment conducted immediately before intervention was finalized, the first intervention session began. Each subject participated in six intervention sessions. The number of intervention sessions were considered based on findings in earlier studies which had shown that 5 or 6 days of stimulation would be effective for a tDCS intervention [4, 6, 8, 26-28]. After the last intervention session, immediately post-intervention assessments were carried out and one week later, the second post-intervention assessments were conducted. Afterwards, to investigate the maintenance of the treatment gains, post-intervention assessments were done six weeks after treatment termination. This single-center trial was conducted at the Vahdat Neurorehabilitation Clinic in Tehran, Iran.

Transcranial Direct Current Stimulation

Participants underwent anodal or sham tDCS according to the group they were randomly assigned to. An EEG cap was used to identify the site of stimulation. The anode electrode was positioned over the left superior temporal gyrus (T3 according to the 10-20 international system [29]), and the cathode electrode was placed over the right frontopolar region (Fp2 according to 10-20 system [29]). The electrode positions were fixed by elastic rubber straps. In the anodal group, stimulation was done by passing 1 mA current between two 5cm x 7cm electrodes for a duration of 20 minutes with ramp up and ramp down intervals of 15 seconds. This setup was shown to be efficient for enhancing speech fluency in other tDCS studies [4, 30]. A neuroConn DC-STIMULATOR was used to deliver tDCS. We used conductive rubber electrodes encased in a sponge pocket. Physiological saline solution was used as an electrolyte-based contact medium. Before placing the electrodes on the scalp, the clinician checked the skin for any skin damage or lesion. For both, anodal and sham modes, the same stimulation intensity parameters were used. However, in the sham group, the duration of stimulation was 30 seconds and the current turned off automatically after 30 seconds.

Delayed Auditory Feedback

In all six intervention sessions, a speech and language pathologist conducted a fluency intervention during stimulation. In this study, DAF was used as a fluency intervention. In order to deliver DAF, Audapter, which is a software package for manipulating the acoustic parameters of speech in real-time, was used [31]. The subjects performed three tasks which included oral reading, monologue, and conversation, under 60-ms delayed auditory feedback. This 60-ms delay has been shown to be efficient to enhance speech fluency in stuttering [32].

Safety and side effects of tDCS were assessed after each intervention session through filling in a 5 point Likert scale (1=very mild, 5=very severe) questionnaire by the participants. The respective questions included potential side effects of tDCS, namely itching, burning, tingling, headache, fatigue, sudden mood change, difficulties to concentrate, change of visual perception, unpleasant somatosensory sensations, unpleasant visual sensations, nausea, drowsiness, feeling that stimulation persisted after the end of intervention, and one open question for any other adverse effects. Furthermore, participants were asked to guess if they received anodal or sham stimulation before any intervention and after the first intervention, as well as after the last interventions, to ensure successful blinding.

Outcome measures

In this study, the mean scores of the percentage of Stuttered Syllables (SS %) served as primary outcome parameter. We obtained 2 baseline measurements, one week, and immediately before intervention, to guarantee symptom stability. At these two pre-intervention time points, the voice of the participants was recorded when performing three different tasks, oral reading, monologue, and conversation. Based on these data, we calculated the primary outcome measure (SS %), which was the average of percentages in those three tasks. A ZOOM H5 handy recorder was used to record the voice of the participants. The same

measurement was taken immediately, one week, and six weeks after the last intervention session (post-intervention assessments). In order to prevent any potential adaptation effect, different reading materials and novel monologue and conversation topics were used in each assessment and intervention session. The mean score of SS% at the three post-intervention time points in the intervention group was expected to be significantly lower than that in the sham group (the lower score of SS% represents the less severe stuttering). Also, no significant difference was expected between groups at either of the baseline time points.

Secondary outcomes were the score of Stuttering Severity Instrument-4 (SSI-4), as well as the score of the Overall Assessment of Speaker's Experience of Stuttering (OASES). In the two pre-intervention assessments, the principal investigator observed physical behavior (such as distracting sounds, facial grimaces, head movements, and arm and leg movements) which was required to calculate the score of the SSI-4. In addition, participants filled out the OASES questionnaire which is a self-report assessment tool, as the secondary outcome measure. After the second baseline assessments, the intervention was started, and was carried out over six consecutive days. The similar results of SS% scores were expected for SSI-4 and OASES scores in both study groups at different time points.

Randomization

Participants were randomly allocated to intervention and control groups. The random assignment of the participants prevented selection bias and dysbalanced confounding factors between the study arms. A computer-generated randomization method was used via the website www.randomization.com. We determined 50 subjects and four blocks of equal size to generate a random list. Each participant was given a unique ID and was assigned to one of the experimental groups. The person responsible for generating the random list was not involved in any other part of the trial.

Blinding

This study was double-blind. Neither the participants nor the investigators knew which group (anodal or sham) each participant was assigned to. A sealed opaque envelope method was used for the purpose of concealment. A clinician was given randomly generated treatment allocations within sealed opaque envelopes. Once a participant consented to enter the trial, an envelope was opened and the participant was then allocated to one of the intervention groups. Researchers who were responsible for outcome assessment and data analysis were also masked to the group assignment.

In order for the procedure to be confirmed as a blinding one, before any intervention and after the first intervention as well as after the last session, participants were asked which type of treatment they thought to receive, anodal tDCS or sham.

Statistical methods

All statistical analyses were performed using SPSS Statistics V22.0 and Stata 15. A sample size of 25 participants per group (50 participants in total) was estimated based on the previous study by Chesters and colleagues [4], and using G*Power software [33]. The determination of sample size was based on two criteria which were to detect a significant difference for the relevant time × group interaction in the primary statistical test and to have an effect size of f= 0.17. Data were analyzed by a 2-way mixed model ANOVA with the within-subject factor time, the between-subject factor group (anodal/sham tDCS), and the dependent variable stuttered syllables (SS %). The α and β errors were set at 0.05 and 0.20, respectively.

Two experienced raters independently counted the SS% of all speech samples. Cohen's kappa coefficient was used to measure inter-rater reliability.

Data were analyzed by the intention-to-treat (ITT) and modified intention-to-treat (mITT) approaches. In order to test the assumption that data distribution was normal, Kolmogorov-Smirnov (K-S) and Shapiro-Wilk tests were performed. These results are presented in Table 1.

Demographic as well as baseline characteristics, and primary and secondary outcomes were assessed by descriptive statistics including measures of mean, standard deviation, median, minimum, and maximum for quantitative variables, and frequency and percentage for qualitative variables. The characteristics of the participants and demographic variables in the two groups were compared at the baseline using *Student's* t-tests in case of quantitative, and the chi-square test for the qualitative variables.

The effect of anodal tDCS on SS % (the primary outcome) was assessed by a 2-way mixed-model ANOVA with the percentage of stuttered syllables as the dependent variable, the between-subject factor tDCS (anodal vs. sham), and the within-subject factor time (one week and immediately before the intervention, immediately, one week after, and six weeks after the intervention). Where statistically significant time × group interactions were found in the results of the ANOVA, exploratory post-hoc *Student´s* t-tests were performed to identify significant differences for each time point between the two groups. The Bonferroni correction was performed for all reported p-values. For the secondary outcome measurements (SSI-4 and OASES scores), the same procedures were conducted.

Adverse effect questionnaire data were analyzed using a 2-way mixed-model ANOVA. A chi-square test was performed to assess successful blinding.

Results

Fifty people (Mean=26.92 year, SD=6.23) with moderate to severe stuttering met the inclusion criteria and were enrolled in the study. No drop-out occurred and all participants completed all intervention and post-assessment sessions. In order to determine inter-rater reliability, two experienced raters independently counted the SS% of all speech samples and Cohen's kappa was calculated. The strong intraclass correlation coefficient (ICC) for the inter-rater agreement (ICC=0.95, p<0.05) indicated high rating reliability.

Demographic and baseline characteristics of the participants are reported in Table 2. For this report, the data from the first baseline time point was used. The study groups were well-matched based on the examination of the demographic variables.

Comparison of the primary outcome measure mean of SS% for two baselines time points and immediately, one week, and six weeks after the treatment resulted in a significant main effect of the group ($F(1,49)=65.95$, $p=0.001$, $=0.85$; Figure 1). The results also showed that the interaction between time and group was significant ($F(1, 48) =74.41$, $p=0.001$, $=0.77$). The results of the post-hoc tests showed that the mean of SS% in the anodal tDCS group were significantly lower than that in the sham group at the three post-intervention time points (Table 3).

The results of the SSI-4 (one of the secondary outcome measures) which was assessed at the same five assessment points (one week and immediately before the intervention as the baseline, and immediately, one week and six weeks after the intervention) showed a significant main effect of group ($F(1, 49) =59.62$, $p=0.001$, $=0.52$; Figure 2), and a significant time × group interaction as well ($F(1, 48) =123.55$, $p=0.001$, $=0.72$). For the between-group comparisons, the results of post-hoc tests showed that at the three post-intervention time points, the SSI-4 scores in the anodal tDCS group were significantly lower than that in the sham group. These findings are shown in Table 3.

The other secondary outcome measure was the OASES score, which also was assessed at the same five assessment points (one week and immediately before the intervention as the baseline, and immediately, one week and six weeks after the intervention). We found no statistically significant main effect of the group ($F(1, 49) =0.28$, $p=0.60$, $=0.006$; Figure 3), but a significant interaction between time and group ($F(1, 48) =67.20$, $p=0.001$, $=0.58$). For the between-group comparisons, no significant differences were found in the overall OASES scores (Table 3). For the within-group comparisons, OASES scores significantly decreased in the anodal tDCS groups for the post intervention time point 5 (six weeks after the intervention) compared to the first baseline time point ($t=-6.21$, $p=0.001$). No significant difference was observed between 5 time points in the sham group.

The results of the adverse effect questionnaire analysis showed no significant main effects of the group ($F(1, 49) =2.76$, $p=0.07$), or the time ($F(1, 5) =1.78$, $p=0.17$), and no significant time × group interaction as well ($F(1, 48) =6.46$, $p=0.06$). Adverse effects were limited to mild and very mild symptoms such as itching and burning sensation at the application sites.

In order to investigate successful blinding, a chi-square test was applied. The findings indicated no significant difference between the two groups with respect to guessing the intervention condition ($\chi^2(1, N=50) = 0.08$; $p= 0.77$).

Discussion

We conducted a randomized controlled trial with follow-up measures to explore the effectiveness of tDCS combined with DAF to improve speech fluency in adults who stutter. The impact of the combined

treatment on symptoms was evaluated by SS% as primary outcome parameter. Maintenance of the treatment outcomes was examined for up to six weeks to exclude only short-lasting effects with limited clinical value [2]. The results showed that SS% was significantly lower in the anodal tDCS group as compared to the sham group at the three post-intervention assessments. Additionally, the effect size (Cohen's d>0.8) shows a large effect of this intervention.

In addition, we obtained the SSI-4 score before and after the treatment. This score includes additional information, such as changes in the duration of stutter moments and physical concomitants of stuttering. These parameters disrupt speech fluency and have negative effects on communication. Reduction of respective behaviors, as expected, leads to enhancement of communication effectiveness in adults who stutter [24]. The SSI-4 score was significantly lower in the anodal group, as compared to the sham group at the three post-intervention assessments. These findings are consistent with those of the primary outcome measure.

Finally, we surveyed the impact of the clinical effect of the intervention on the psycho-social impact of living with stuttering by the OASES questionnaire. This questionnaire measures the effect of stuttering on four different aspects, namely general information, reactions to stuttering, communication in daily situations, and quality of life [25]. The results show no statistically significant difference in the total OASES scores between the two study groups. However, the within-group analysis shows that there was a significant reduction of OASES score at the six weeks after intervention assessment as compared to the baseline in the anodal tDCS group. This reduction was mainly caused by the general information subscore of the OASES questionnaire, and may be due to additional information about possible causes of stuttering, factors affecting stuttering, and potential treatment methods delivered to the participants during the course of study.

The results of this study show that anodal tDCS can increase speech fluency for a prolonged time course after the intervention, when combined with fluency therapy. The direction of these results is consistent with previous studies in stuttering [4], as well as the tDCS studies in which the impact of stimulation on other speech-related symptoms was explored [10, 34, 35]. In summary, our findings propose anodal tDCS as an adjunctive method to increase speech fluency in stuttering, particularly in adults whose behavioral treatments have failed.

It should be noted that different stimulation protocols, for example varying electrode placement and current intensity, can differentially affect the outcomes of tDCS combined with fluency intervention. In this study, the left superior temporal gyrus was stimulated by anodal tDCS. In aphasia, some studies showed that bi-hemispheric tDCS stimulation improves the motor and articulation functions [36-38]. So, future studies could investigate the effect of bilateral or right superior temporal gyrus stimulation. In addition, tDCS is commonly delivered with current intensity ranging from 1 to 2 mA [39]. There is an assumption that higher intensity will have a stronger effect on cortical excitability [16, 21]. This more intensive current was used in clinical and cognitive studies [40-42], but the evidence about its physiological effects is limited. Thus, the current intensity of 2 mA could be investigated in future studies.

Moreover, because of the size of electrodes which were used in this study, it is possible that the middle and inferior temporal gyrus and even inferior frontal gyrus in addition to superior temporal gyrus were stimulated. So, the effect may be non-specific.

In this study, a combination of behavioral intervention and tDCS was used. The effect of tDCS alone could be investigated in future studies. Adding functional neuroimaging methods in future studies would be valuable to provide mechanistic information about the mode of action of the intervention. Additionally, further studies are needed to investigate whether an extension of interventions would result in stronger effects (better improvement of fluency) and/or longer lasting positive outcomes of the treatment.

Conclusions

The results of this study showed an adjunctive effect of tDCS, when combined with DAF, on stuttering. The combined intervention led to a significant lower percentage of stuttered syllables and SSI-4 scores in the tDCS group as compare to the sham group.

Abbreviations

tDCS: transcranial Direct Current Stimulation; DAF: Delayed Auditory Feedback; SS %: percentage of Stuttered Syllables; SSI-4: Stuttering Severity Instrument-Forth Edition; OASES: Overall Assessment of the Speaker's Experience of Stuttering

Declarations

Registration

This trial was registered in ClinicalTrial.gov before recruiting the subjects. The registration number is NCT03990168 and the date of registration is June 18, 2019.

Protocol

The protocol article of this study has been accepted in the JMIR research and protocols journal [43].

Funding

Iran University of Medical Sciences funded this work.

Ethics approval and consent to participate

This study was carried out in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran and has the approval ID of IR.IUMS.REC.1398.352 of the Iran National Committee for Ethics in Biomedical Research.

Consent for publication

Although the investigators are free to use the study findings for educational and scientific purposes, prior to submission of the manuscript, written consent was obtained from the study sponsor. Any information about subjects is kept confidential and not available for public access. In addition, any document, data, voice recording, and other records are coded by a participant identification number, and the subject names are kept confidential.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

MN is at the scientific advisory boards of Neuroelectrics, and NeuroDevice. The other authors declare that they have no competing interest. This study has received assistance from Iran National Science Foundation and has undergone peer-review by the funding body.

Authors' contributions

RM, RR, and MN contributed to the conception **and** design of the study. AK and RZ contributed in analyzing and interpretation of the data. AO wrote the MATLAB code. NM was a major contributor in writing the manuscript and collecting the data. MN substantively revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all of the participants who took part in this study. We would also like to thank the Iran National Science Foundation for supporting this trial.

References

1. Bloodstein, O. and N.B. Ratner, *A handbook on stuttering Clifton Park, NY: Thomson Delmar Learning; 2008.* A Handbook on Stuttering.

2. Guitar, B., *Stuttering: An integrated approach to its nature and treatment*. 2013: Lippincott Williams & Wilkins.
3. Ward, D., *Stuttering and cluttering: frameworks for understanding and treatment*. 2017: Psychology Press.
4. Chesters, J., R. Möttönen, and K.E. Watkins, *Transcranial direct current stimulation over left inferior frontal cortex improves speech fluency in adults who stutter.* Brain, 2018. **141**(4): p. 1161-1171.
5. Thair, H., et al., *Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation.* Frontiers in neuroscience, 2017. **11**: p. 641.
6. Baker, J.M., C. Rorden, and J. Fridriksson, *Using transcranial direct-current stimulation to treat stroke patients with aphasia.* Stroke, 2010. **41**(6): p. 1229-1236.
7. Marangolo, P., et al., *Bihemispheric stimulation over left and right inferior frontal region enhances recovery from apraxia of speech in chronic aphasia.* European Journal of Neuroscience, 2013. **38**(9): p. 3370-3377.
8. Marangolo, P., et al., *Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics.* Behavioural brain research, 2011. **225**(2): p. 498-504.
9. Monti, A., et al., *Improved naming after transcranial direct current stimulation in aphasia.* Journal of Neurology, Neurosurgery & Psychiatry, 2008. **79**(4): p. 451-453.
10. Monti, A., et al., *Transcranial direct current stimulation (tDCS) and language.* J Neurol Neurosurg Psychiatry, 2012: p. jnnp-2012-302825.
11. Chesters, J., *Enhancing speech fluency using transcranial direct current stimulation*. 2016, University of Oxford.
12. Brown, S., et al., *Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies.* Human brain mapping, 2005. **25**(1): p. 105-117.
13. Takaso, H., et al., *The effect of delayed auditory feedback on activity in the temporal lobe while speaking: a positron emission tomography study.* Journal of Speech, Language, and Hearing Research, 2010. **53**(2): p. 226-236.
14. Van Borsel, J., G. Reunes, and N. Van den Bergh, *Delayed auditory feedback in the treatment of stuttering: clients as consumers.* International Journal of Language & Communication Disorders, 2003. **38**(2): p. 119-129.
15. Kalinowski, J., et al., *Self-reported efficacy of an ear-level prosthetic device that delivers altered auditory feedback for the management of stuttering.* International Journal of Rehabilitation Research, 2004. **27**(2): p. 167-170.
16. Nitsche, M.A. and W. Paulus, *Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans.* Neurology, 2001. **57**(10): p. 1899-1901.
17. Nitsche, M.A., et al., *Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human.* Journal of cognitive neuroscience, 2003.

15(4): p. 619-626.

18. Nitsche, M., et al., *Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans.* The Journal of physiology, 2003. **553**(1): p. 293-301.
19. Stagg, C.J., et al., *Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation.* Journal of Neuroscience, 2009. **29**(16): p. 5202-5206.
20. Nitsche, M.A., et al., *Level of action of cathodal DC polarisation induced inhibition of the human motor cortex.* Clinical Neurophysiology, 2003. **114**(4): p. 600-604.
21. Nitsche, M.A. and W. Paulus, *Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation.* The Journal of physiology, 2000. **527**(3): p. 633-639.
22. Budde, K.S., D.S. Barron, and P.T. Fox, *Stuttering, induced fluency, and natural fluency: a hierarchical series of activation likelihood estimation meta-analyses.* Brain and language, 2014. **139**: p. 99-107.
23. Cordes, A.K. and R.J. Ingham, *The reliability of observational data: II. Issues in the identification and measurement of stuttering events.* Journal of Speech, Language, and Hearing Research, 1994. **37**(2): p. 279-294.
24. Riley, G., *SSI-4 stuttering severity instrument fourth edition*. 2009, Austin, TX: Pro-Ed.
25. Yaruss, J.S. and R.W. Quesal, *Overall Assessment of the Speaker's Experience of Stuttering (OASES): Documenting multiple outcomes in stuttering treatment.* Journal of fluency disorders, 2006. **31**(2): p. 90-115.
26. Heth, I. and M. Lavidor, *Improved reading measures in adults with dyslexia following transcranial direct current stimulation treatment.* Neuropsychologia, 2015. **70**: p. 107-113.
27. Khedr, E.M., et al., *Effect of anodal versus cathodal transcranial direct current stimulation on stroke rehabilitation: a pilot randomized controlled trial.* Neurorehabilitation and neural repair, 2013. **27**(7): p. 592-601.
28. Reis, J., et al., *Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation.* Proceedings of the National Academy of Sciences, 2009. **106**(5): p. 1590-1595.
29. Jasper, H., *Report of the committee on methods of clinical examination in electroencephalography.* Electroencephalogr Clin Neurophysiol, 1958. **10**: p. 370-375.
30. Chesters, J., K.E. Watkins, and R. Möttönen, *Investigating the feasibility of using transcranial direct current stimulation to enhance fluency in people who stutter.* Brain and language, 2017. **164**: p. 68-76.
31. Cai, S., et al., *Tensorflow debugger: Debugging dataflow graphs for machine learning.* 2016.
32. Stuart, A., et al., *Investigations of the impact of altered auditory feedback in-the-ear devices on the speech of people who stutter: initial fitting and 4-month follow-up.* International Journal of Language & Communication Disorders, 2004. **39**(1): p. 93-113.
33. Faul, F., et al., *Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses.* Behavior research methods, 2009. **41**(4): p. 1149-1160.

34. Holland, R. and J. Crinion, *Can tDCS enhance treatment of aphasia after stroke?* Aphasiology, 2012. **26**(9): p. 1169-1191.
35. Sandars, M., L. Cloutman, and A.M. Woollams, *Taking sides: an integrative review of the impact of laterality and polarity on efficacy of therapeutic transcranial direct current stimulation for anomia in chronic poststroke aphasia.* Neural plasticity, 2016. **2016**.
36. Marangolo, P., et al., *Bilateral transcranial direct current stimulation language treatment enhances functional connectivity in the left hemisphere: preliminary data from aphasia.* Journal of Cognitive Neuroscience, 2016. **28**(5): p. 724-738.
37. Bolognini, N., et al., *Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients.* Neurorehabilitation and neural repair, 2011. **25**(9): p. 819-829.
38. Lindenberg, R., et al., *Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients.* Neurology, 2010. **75**(24): p. 2176-2184.
39. Nitsche, M.A., *Safety criteria for transcranial direct current stimulation (tDCS) in humans.* Clin Neurophysiol, 2003. **114**: p. 2220-2222.
40. Bueno, V.F., et al., *Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression.* Neurocase, 2011. **17**(4): p. 318-322.
41. Brunoni, A., et al., *Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2011. **35**(1): p. 96-101.
42. Ferrucci, R., et al., *Transcranial direct current stimulation in severe, drug-resistant major depression.* Journal of affective disorders, 2009. **118**(1-3): p. 215-219.
43. Moein, N., et al., *Delayed Auditory Feedback and Transcranial Direct Current Stimulation Treatment for the Enhancement of Speech Fluency in Adults Who Stutter: Protocol for a Randomized Controlled Trial.* JMIR Research Protocols, 2020. **9**(4): p. e16646.

Tables

Table 1 Skewness, kurtosis, and Normality Tests for primary and secondary outcomes

Variable	N	Skewness	Kurtosis	K-S [a] a With Lilliefors Correction Test			Shapiro-Wilk Test		
				Statistics	Df [a]	*P* value	Statistics	Df [a]	*P* value
SS%	50	0.4	-0.47	0.11	50	0.2	0.95	50	0.09
SSI-4 score	50	0.81	0.65	0.1	50	0.21	0.94	50	0.13
OASES score	50	-0.25	-0.38	0.16	50	0.1	0.89	50	0.07

[a] Abbreviations: Df, Degree of freedom; K-S, Kolmogorov-Smirnov

Table 2 Demographic and baseline characteristics

Stimulation		Mean	SD	Median	Minimum	Maximum
Anodal (n=25)	Sex (Female %)	12(48%)				
	Age	26	6.55	25	17	47
	SS%	8.38	2.53	7.66	4.33	14.33
	SSI-4	32.84	4.72	32	25	46
	OASES	61.02	10.93	63.60	39.40	78.60
Sham (n=25)	Sex (Female %)	13(52%)				
	Age	26.50	5.77	26	19	38
	SS%	8.45	3.36	8	3.67	14.33
	SSI-4	32.08	3	31	26	36
	OASES	58.93	14.30	59.60	38.40	74.80

Table 3 Primary and Secondary outcomes distributions in pre and post-intervention assessments by trial groups (Bonferroni-adjusted)

variable	Time point	Anodal group n=25	Sham group n=25	Cohen's d (95% CI)	P value
SS%	Time point 1	8.38 (2.53)	8.45 (3.36)	-0.02 (-0.57, 0.53)	0.92
	Time point 2	8.40 (2.59)	8.40 (3.30)	0.001 (-0.55, 0.55)	0.99
	Time point 3	4.74 (1.62)	6.81 (2.54)	-0.97 (-1.55, -0.37)	0.03
	Time point 4	5.26 (1.68)	8.29 (3.42)	-1.12 (-1.71, -0.52)	0.005
	Time point 5	5.36 (1.67)	8.45 (3.35)	-1.16 (-1.76, -0.56)	0.005
SSI-4 score	Time point 1	32.84 (4.72)	32.08 (3)	0.19 (-0.36, 0.74)	0.50
	Time point 2	32.88 (4.51)	31.96 (3.04)	0.23 (-0.31, 0.79)	0.42
	Time point 3	27.64 (4.94)	30.48 (2.87)	-0.70 (-1.27, -0.12)	0.01
	Time point 4	27.68 (5.14)	31.68 (2.96)	-0.95 (-1.53, -0.36)	0.001
	Time point 5	27.96 (5.02)	31.92 (3.08)	-0.95 (-1.53, -0.36)	0.001
OASES score	Time point 1	61.02 (10.93)	58.93 (14.30)	0.16 (-0.39, 0.71)	0.06
	Time point 2	61.48 (11.01)	57.89 (13.90)	0.28 (-0.27, 0.84)	0.07
	Time point 3	60.22 (10.95)	57.01 (14.06)	0.25 (-0.30, 0.81)	0.06
	Time point 4	60.55 (11)	57.22 (14.06)	0.26 (-0.29, 0.81)	0.06
	Time point 5	53.91 (11.57)	56.75 (14.10)	-0.22 (-0.77, 0.33)	0.87

Time point 1= One week before intervention, Time point 2= Immediately before intervention, Time point 3= Immediately after intervention, Time point 4= One week after intervention, and Time point 5= Six weeks after intervention

Figures

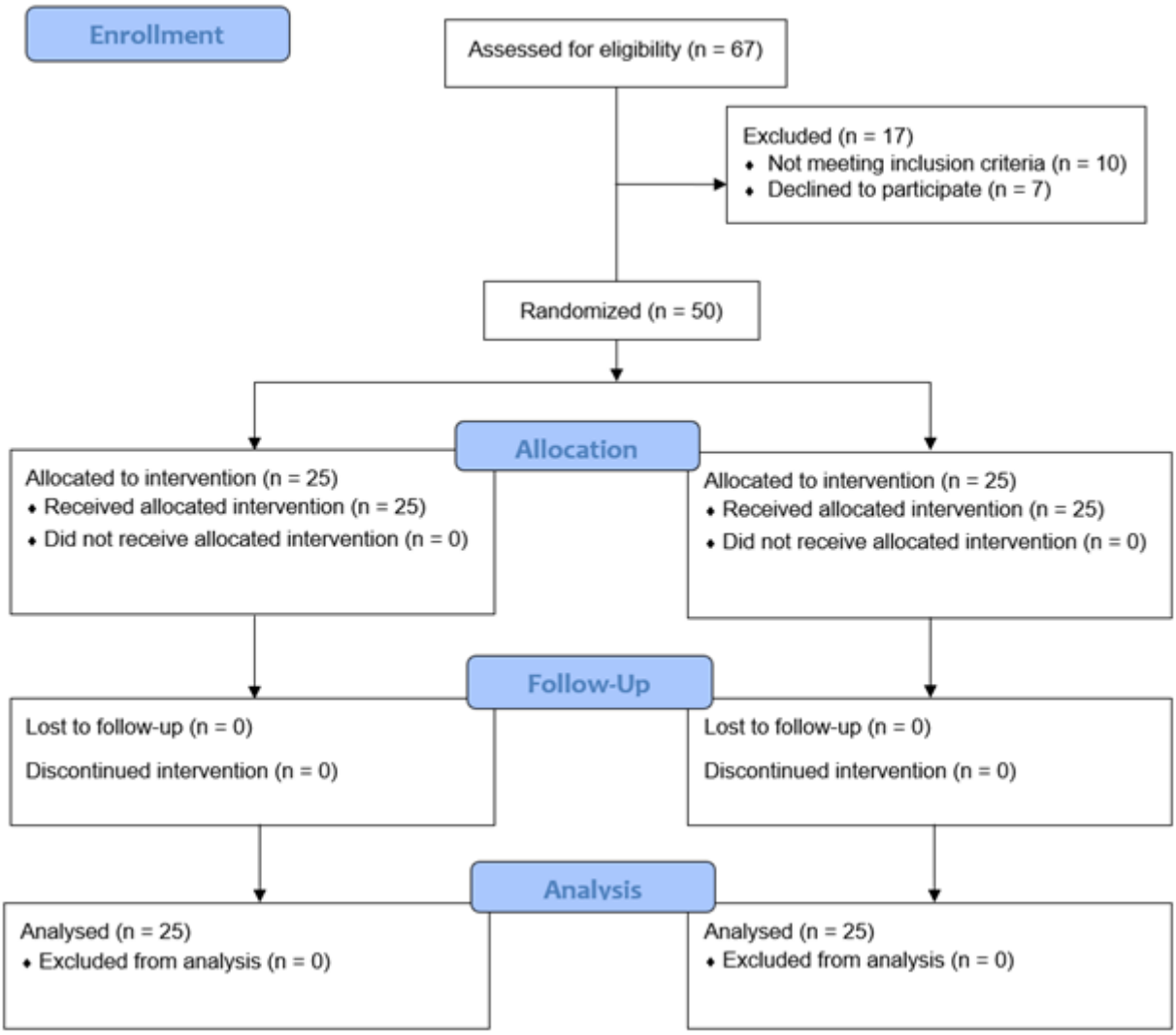

Figure 1

CONSORT flow chart of the study. The study was registered at URL: https://clinicaltrials.gov/ct2/show/NCT03990168 (ID= NCT03990168)

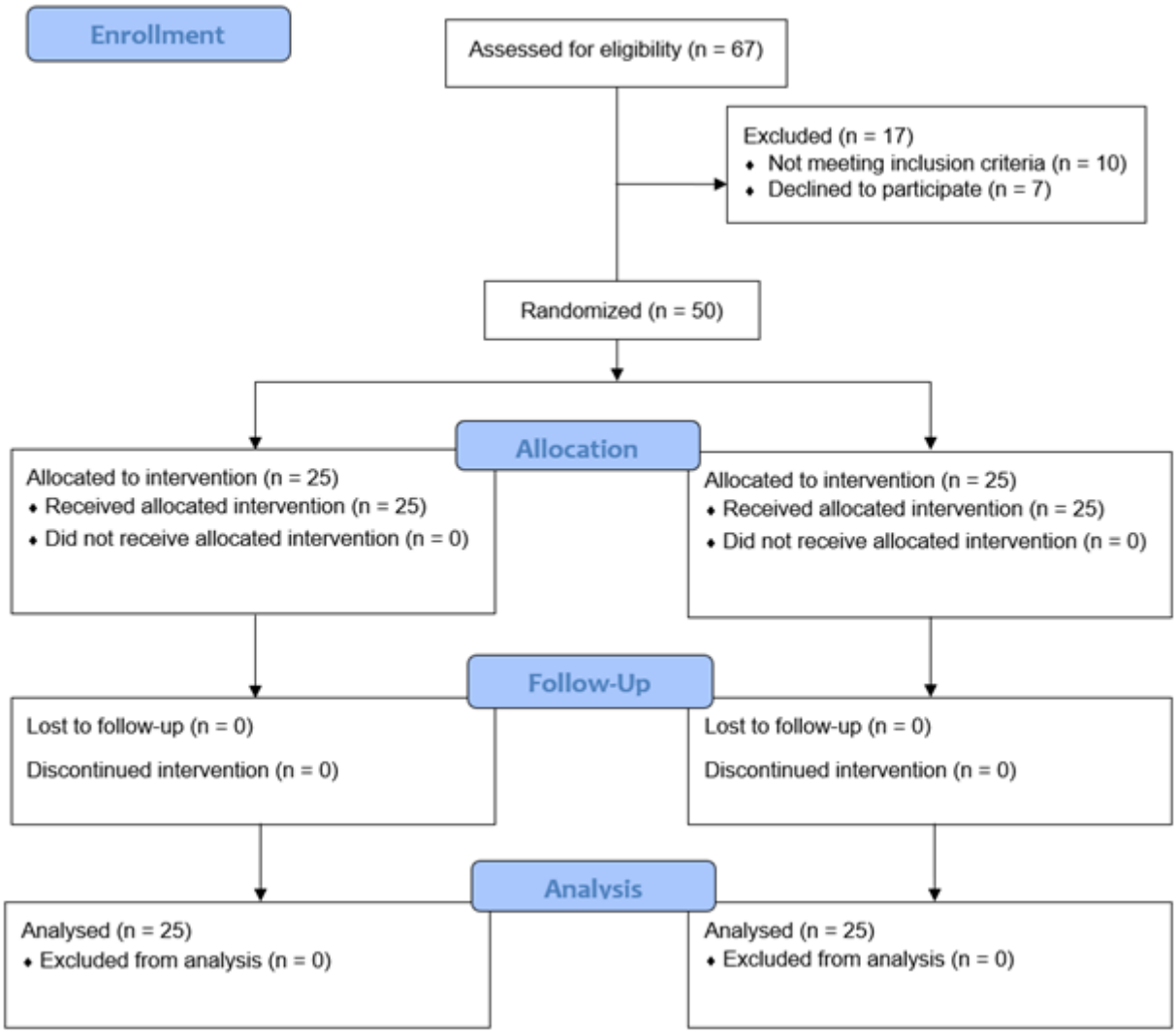

Figure 1

CONSORT flow chart of the study. The study was registered at URL: https://clinicaltrials.gov/ct2/show/NCT03990168 (ID= NCT03990168)

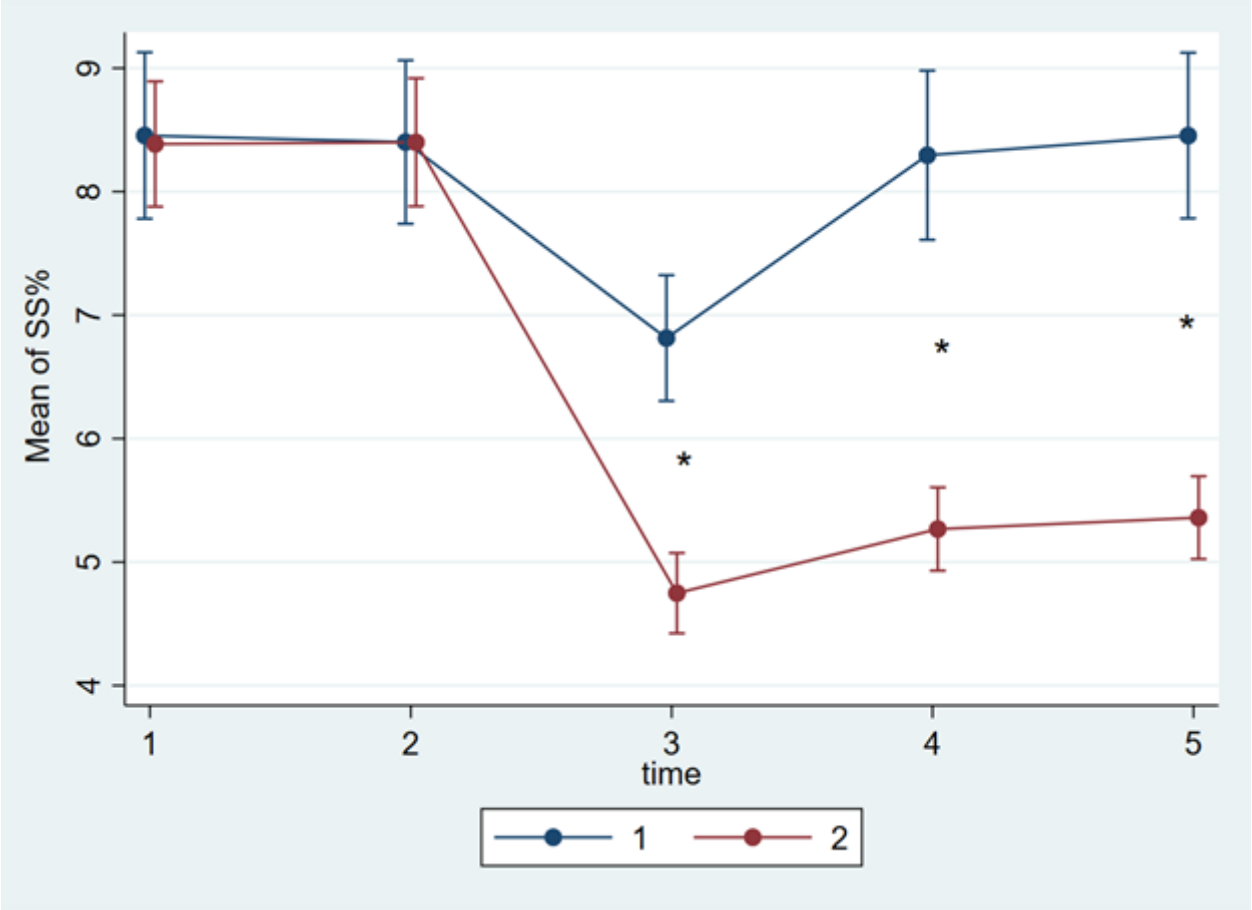

Figure 2

Effect of anodal tDCS on percentage of Stuttered Syllables (primary outcome measure). Lines show the mean of SS% measured at two baseline points as pre-intervention assessments and 3 post-intervention points (immediately, one week, and six weeks after treatment). For SS%, higher scores indicate larger severity. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group). The asterisks mark significant differences between the real and sham stimulation groups.

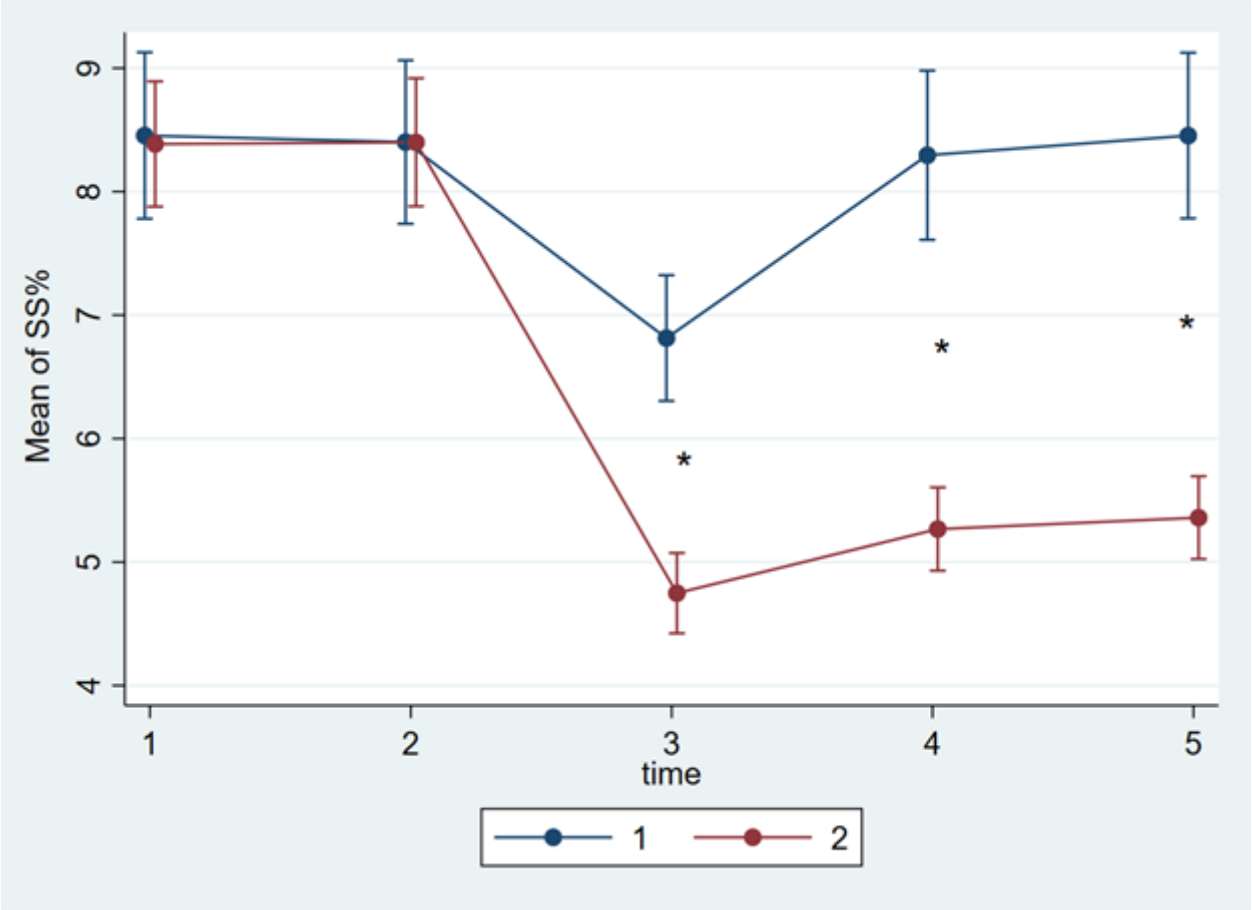

Figure 2

Effect of anodal tDCS on percentage of Stuttered Syllables (primary outcome measure). Lines show the mean of SS% measured at two baseline points as pre-intervention assessments and 3 post-intervention points (immediately, one week, and six weeks after treatment). For SS%, higher scores indicate larger severity. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group). The asterisks mark significant differences between the real and sham stimulation groups.

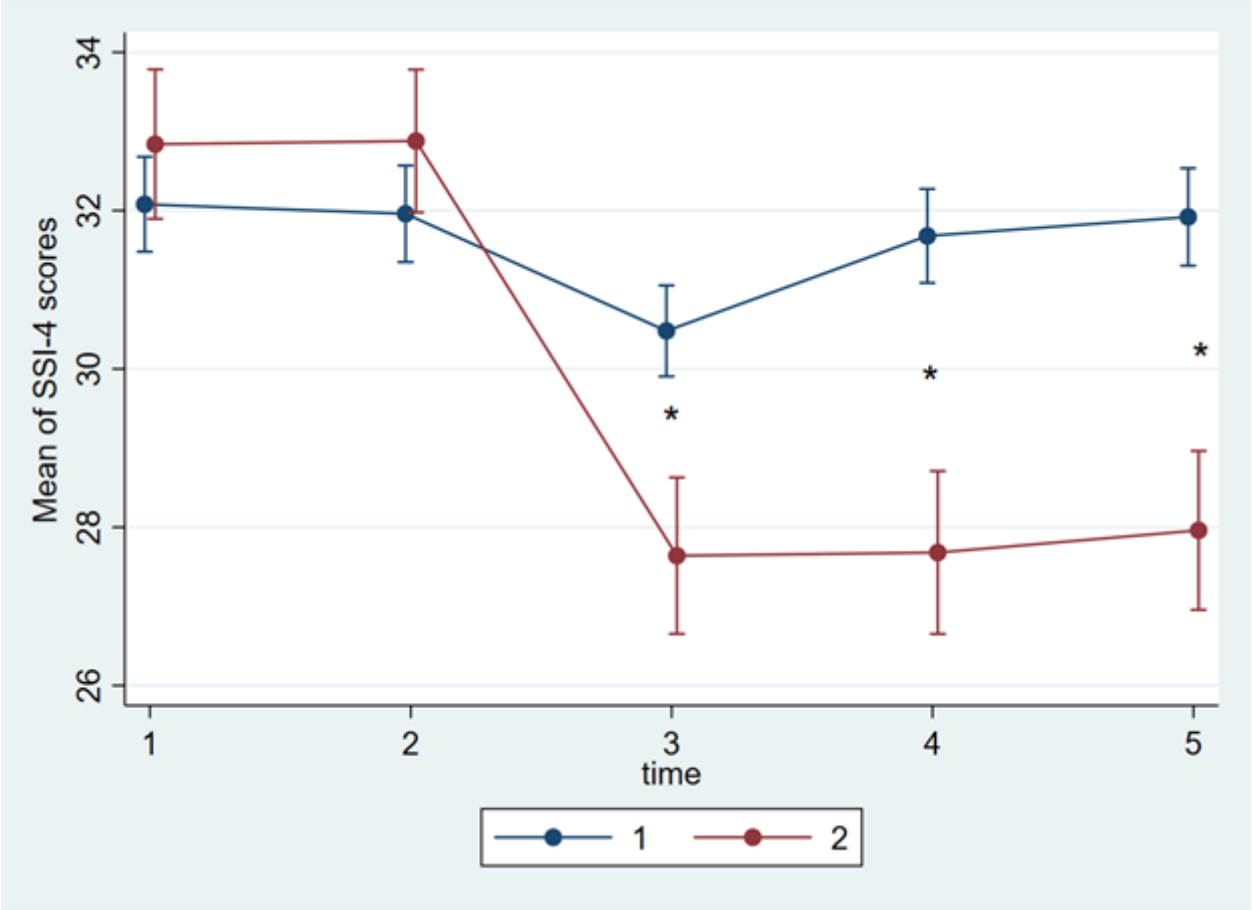

Figure 3

Effect of anodal tDCS on the SSI-4 score (secondary outcome measure). Lines show the SSI-4 scores measured at two baseline points as pre-intervention assessments and 3 post-intervention points (immediately, one week, and six weeks after treatment). The range of SSI-4 score is from 0 to 56, higher scores indicate larger severity. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group). The asterisks mark significant differences between the real and sham stimulation groups.

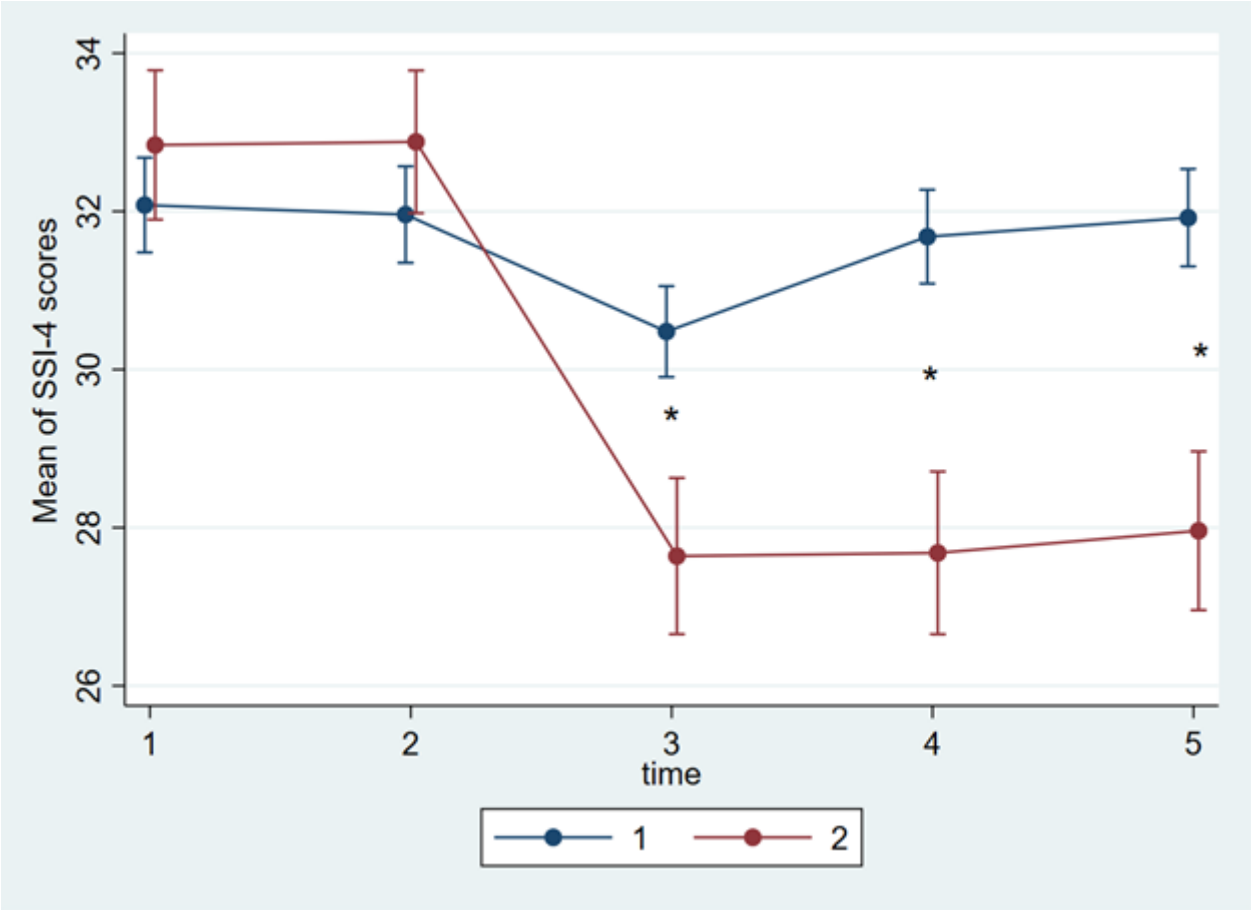

Figure 3

Effect of anodal tDCS on the SSI-4 score (secondary outcome measure). Lines show the SSI-4 scores measured at two baseline points as pre-intervention assessments and 3 post-intervention points (immediately, one week, and six weeks after treatment). The range of SSI-4 score is from 0 to 56, higher scores indicate larger severity. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group). The asterisks mark significant differences between the real and sham stimulation groups.

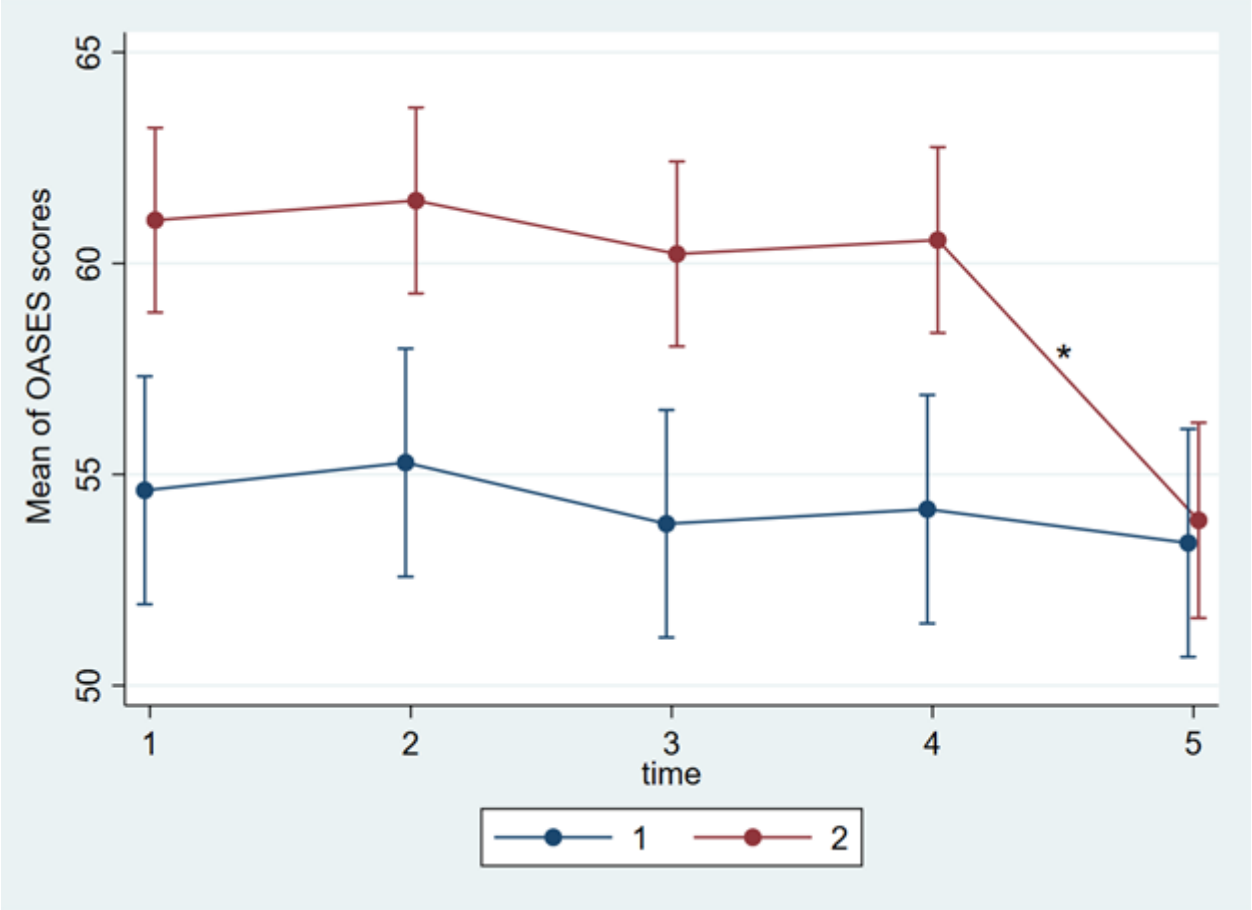

Figure 4

Effect of anodal tDCS on the OASES score (secondary outcome measure). Lines show the OASES scores measured at two baseline points as pre-intervention assessments and three post-intervention time points (immediately, one week, and six weeks after treatment). The range of OASES score is from 20 to 100, higher scores indicate more negative experiences. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group).

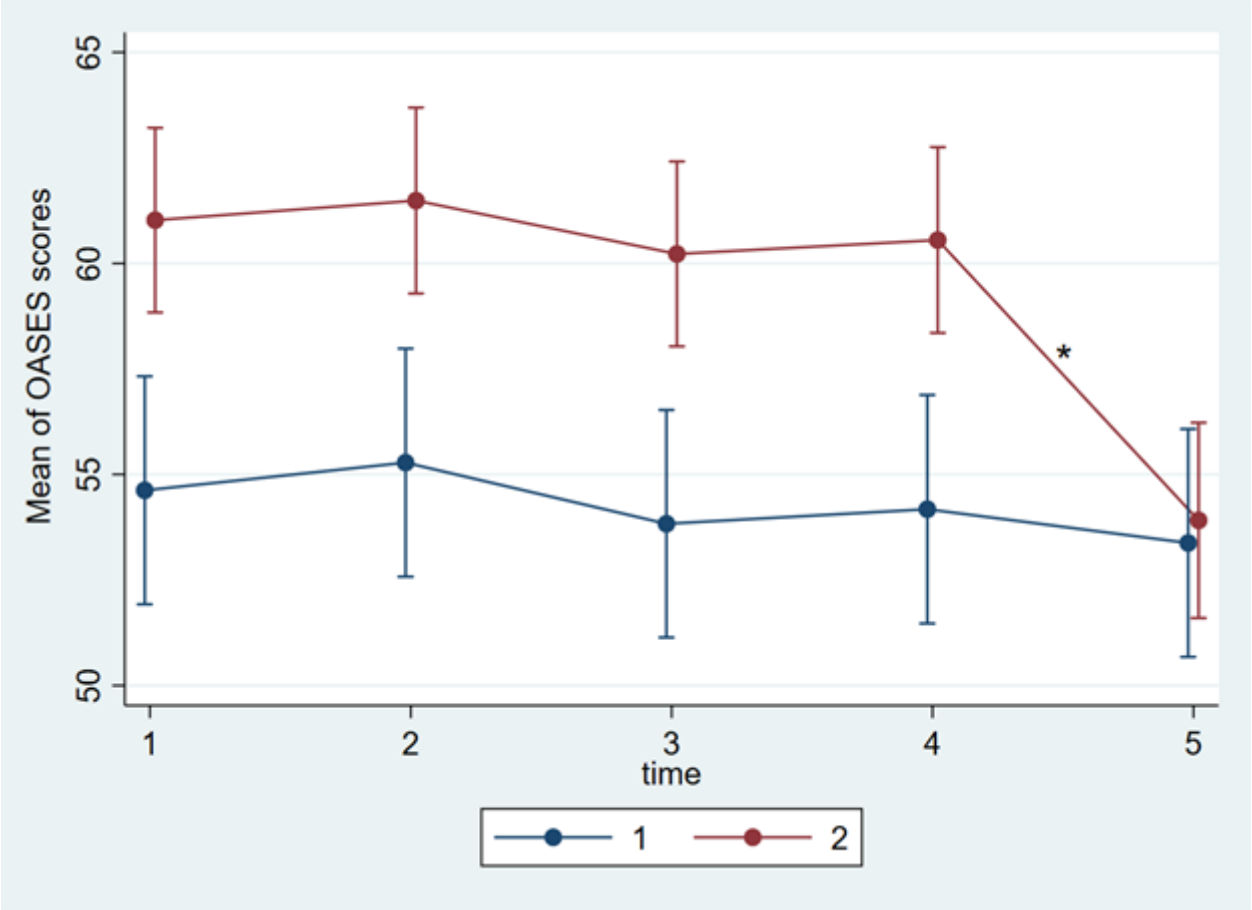

Figure 4

Effect of anodal tDCS on the OASES score (secondary outcome measure). Lines show the OASES scores measured at two baseline points as pre-intervention assessments and three post-intervention time points (immediately, one week, and six weeks after treatment). The range of OASES score is from 20 to 100, higher scores indicate more negative experiences. Error bars indicate standard error of the mean (SEM) (1=Sham group, 2=Anodal group).