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The effect of bi-hemispheric transcranial direct current stimulation on verbal function in Broca's aphasia

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ABSTRACT

Aphasia is one of the most common deficits occurring after stroke that remains, at least in part, even after speech therapy and medication treatment. Non-invasive direct current transcranial stimulation (tDCS) is used to improve brain function by induction of neural plasticity. This study investigated the effect of bi-hemispheric tDCS on verbal function in patients with stroke-induced Broca's aphasia.

Thirty patients with Broca's aphasia due to ischemic stroke, referred to an academic hospital in Guilan Province, Iran, in 2019-20, were studied. Patients were divided into two groups receiving seven sessions of either active or sham tDCS. The tDCS sessions began 10–20 days after stroke onset. The severity of aphasia before and after the intervention and a 3-month follow-up were assessed by the Persian version of the Western Battery-1 test (P-WAB-1). T-test, ANOVA, and Repeated Measurement were used for data analyses.

The mean P-WAB-1 score was significantly higher in the intervention group both early after tDCS ($P \leq 0.0001$) and on the 3-months follow-up ($P \leq 0001$). Linear regression analysis indicated that tDCS had a positive effect on verbal performance scores independent of age, sex, and lesion volume (Regression coefficient = −33.3).

Bi-hemispheric tDCS effectively improves verbal function in Broca's aphasia in the sub-acute phase of ischemic stroke.

1. Introduction

Stroke is the second leading cause of death worldwide and one of the most important causes of disability and death in developed and developing countries with an increasing incidence (Wang et al., 2017). Annually, 16 million people suffer from stroke globally (Wood et al., 2016).

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One of the most common and debilitating cognitive disorders caused by stroke is aphasia, which affects nearly 80,000 new cases annually in the United States and 6.4 million people. Aphasia occurs in 31–38% of acute stroke cases (Norise, Sacchetti, & Hamilton, 2017). Broca's aphasia is a common type of aphasia with a prevalence of 12% among different types of aphasia caused by the first stroke. Some extents of spontaneous recovery, especially in the first 2–3 months after stroke, are seen in most patients (Hamilton, Chrysikou, & Coslett, 2011). However, some chronic deficits persist in many patients with post-stroke aphasia (Marangolo, 2000).

As current treatments such as speech therapy and medications prescribed for patients with aphasia are not effective enough, new alternative treatment methods are needed to improve aphasic patients (You, Kim, Chun, Jung, & Park, 2011). Recently, clinical use of direct current transcranial stimulation (tDCS) has been suggested to facilitate recovery after stroke (Shah-Basak et al., 2015). Although there are many reports regarding the effects of tDCS on different aspects of verbal communication in stroke-induced aphasia (Marangolo, 2020), its effectiveness is still controversial; for instance, Volpato et al. observed no significant difference in action and object naming abilities between the sham and active tDCS patients (Volpato et al., 2013). Also, most of the supporting literature has used active tDCS protocols in combination with different behavioral therapies (ALHarbi, Armijo-Olivo, & Kim, 2017), which can bias the net effect of tDCS. On the other hand, the tDCS protocol (stimulus intensity and duration, electrode location, etc.) varies in different studies; the number of tDCS sessions is reported from 1 to 30, mainly with an intensity of 1–2 mA for 10–30 min (Marangolo, 2020). The site of stimulation varies in an extensive range of area from the left or right dorsolateral prefrontal cortex (DLPFC) (Shah-Basak et al., 2015), inferior frontal gyrus (IFG) (Marangolo, Fiori, Di Paola et al., 2013) to the cerebellar cortex (Marangolo, Fiori, Caltagirone, Pisano, & Priori, 2018), and thoracic spinal vertebrae (Marangolo et al., 2017). Some studies have reported improved verbal function after tDCS in which the excitatory (anodic) active electrode was placed on the left hemisphere to boost the activity of the perilesional areas (Baker, Rorden, & Fridriksson, 2010; Vestito, Rosellini, Mantero, & Bandini, 2014), while others implemented inhibitory (cathodic) tDCS on the contralateral hemisphere to suppress its maladaptive activity (Kang, Kim, Sohn, Cohen, & Paik, 2011; Shah-Basak et al., 2015). In the present study, bi-hemispheric tDCS was applied for simultaneous anodic excitation of the lesioned hemisphere and cathodic inhibition of the contralateral hemisphere in patients with stroke-induced Broca's aphasia in the sub-acute phase.

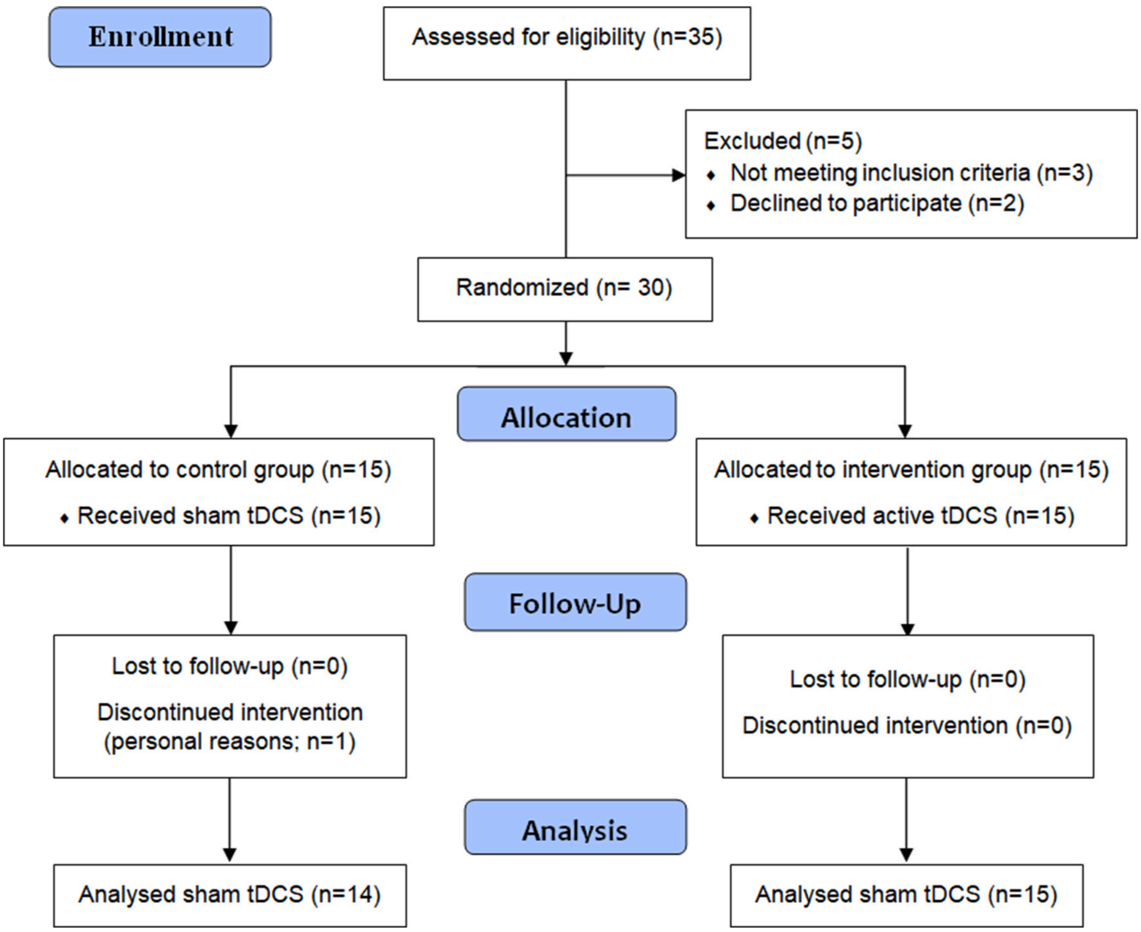

Fig. 1. The Flowchart of the enrollment to the study.

2. Materials and methods

A prospective, parallel randomized, double-blind clinical trial was performed at Guilan University of Medical Sciences, Rasht, Iran. A total of 35 patients with post-stroke Broca's aphasia, referred to the department of neurology at Poursina hospital of Rasht (Iran), were recruited for examination two weeks after the stroke. Patients, who met the inclusion criteria, entered the study after obtaining written informed consent. As shown in the Consort flowchart in Fig. 1, finally, 30 patients were enrolled for block randomization. Sampling was performed gradually from October 2019 for 14 months from all eligible patients. The study received ethical approval from the Research Ethics Committee-Guilan University of Medical Sciences (IR.GUMS.REC.1398.069). Upon ethical approval, the study was registered at the Iranian Registry for Clinical Trials (Reference number: IRCT20190522043673N1). The sample size required for the effectiveness of the proposed therapeutic approach for the improvement of aphasia was calculated based on the results of previous studies (Wu, Wang, & Yuan, 2015); taking into account a confidence level of 95% and test power of 80% by employing the following equation, 15 people in each group was estimated.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \, (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Inclusion criteria consisted of Broca's aphasia caused by sub-acute ischemic stroke (8–20 days after stroke onset) and diagnosed according to the Persian version of the Western Battery-1 (P-WAB-1) test with a score of lower than 92, age of 18–80 years, having the ability to speak, read and write in Persian (before the stroke), right-handedness, and ability to participate in the treatment process.

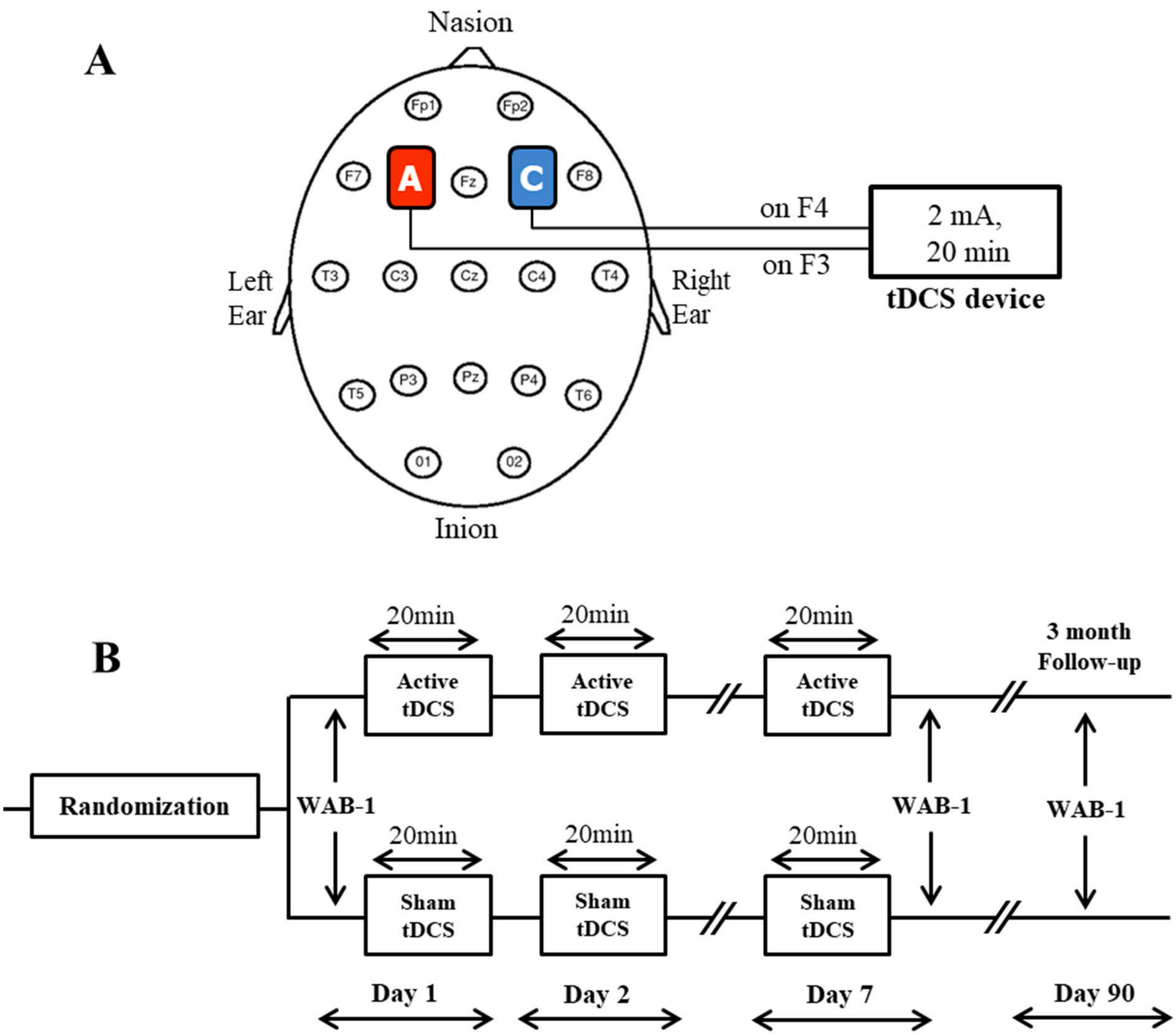

Fig. 2. Experimental procedure. The anode and cathode electrodes were respectively placed on F3 and F4 regions according to the international 10–20 system (A). The timeline of the experimental procedure (B).

Exclusion criteria were hemorrhagic stroke, contraindications to brain stimulation including metal implants in the brain, cardiac pacemaker, pregnancy, use of sodium and calcium channel blockers, psychoactive or CNS-effective drugs, alcohol and drug abuse, mental illness or neurological conditions other than stroke, including epilepsy, cerebral palsy, brain trauma, sensitization of the skin under the tDCS electrodes, tDSC-related severe complications, and patient dissatisfaction.

2.1. Randomization and blinding

Block randomization was used with random number sequences employing randomization software (www.sealedenvelope.com). The participants were divided into eight blocks of 4 participants in each.

2.2. Intervention

Prior to the intervention, the size of the lesion caused by stroke was determined based on a brain computed tomography (CT) scan (thickness 7 mm, interval 14 mm, 120 kVp, and 160 mA). The demographic and para-clinical information of the patients were recorded. The intervention was performed with a transcranial direct current stimulation device (OASIS, Mind Alive Company Inc., Alberta, Canada) in the two parallel arms in 7 sessions on consecutive days. In the active tDCS group, electrical stimulation was applied with an intensity of 2 mA for 20 min, while in the sham tDCS group, 2 mA stimulation was applied only for 30 s, and afterward, the intensity was reduced to 0 mA and maintained at the same level for 20 min. The electrode size was 5 × 5 cm, which produced a current density of 0.08 mA/cm^2. As depicted in Fig. 2A, the electrode placement was arranged according to the international 10–20 system; the anode electrode was placed on F3 and the cathode electrode on the F4 region (on the left and right frontal cortices, respectively). Patients' heart rate and blood pressure were measured before and after the intervention. At the end of the intervention, complications such as headache, fatigue, drowsiness, impaired concentration, confusion, redness of the skin, burning, and itching or tingling of the irritated skin were recorded in a questionnaire.

The severity of aphasia was assessed before and at the end of the intervention using the clinical version of the P-WAB-1 test, which assesses the quality of speech content, fluency, auditory comprehension, perception of continuous instructions, the ability to repeat, and naming ability. Each section was given a score from zero to 10 (total score: 0–100). A score of 0–25 indicates very severe; 26–50 shows severe; 51–75 for moderate, and 76–92 for mild cases of aphasia. Patients were re-evaluated after three months based on the verbal performance score, the "aphasia quotient" of the P-WAB-1. The timeline of the experimental procedure is shown in Fig. 2B.

2.3. Statistical analysis

Data were analyzed using SPSS (version 23). The normal distribution of data was assessed by the Shapiro-Wilk test. To compare verbal improvement between the two groups, a *t*-test was used, and the trend of changes was analyzed using repeated measures analysis. Analysis of variance (ANOVA) was also used to compare the changes in test score in active and sham groups at different time points. $P \leq 0.05$ was considered statistically significant.

3. Results

According to the results of the Shapiro-Wilk test, the data was normally distributed. The mean ± SD age of the patients was 64.2 ± 10.7 years with an age range of 35–80 years. Of these patients, 56.7% (n = 17) were female and 43.3% (n = 13) were male. The overall mean ± SD lesion volume was 56.6 ± 41.07 mm^3. The two groups had no significant difference in age, sex, and brain lesion volume (Table 1).

Based on the results shown in Table 2, the difference between the verbal performance test scores of the two groups was significant, and the mean test score increased substantially after the active tDCS procedure in the intervention group. Similar results were obtained using repeated measures analysis ($P = 0.029$). The analysis of covariance showed that the changes in the mean score of the verbal function test before and after the intervention were significant in both groups. The mean of verbal performance was significant between the two groups, even three months after the intervention ($p \leq 0.0001$). Similar results were obtained using repeated measures analysis ($p \leq 0.0001$). As shown in Fig. 3A, the mean difference was greater in the intervention group than in the control group ($p \leq 0.0001$).

The mean P-WAB-1 score was significantly higher in the active tDCS group 3 months after active tDCS in both genders ($p \leq 0.001$). In both age groups, below and above 62 years (the approximate average age of all participants), patients receiving active tDCS had

Table 1
Demographic information of patients with stroke-induced aphasia in sham and active tDCS groups.

Variable	Level	Active tDCS (n = 15)	Sham tDCS (n = 15)	Test statistics	P-value
Age	-	63.07 ± 11.5	65.3 ± 10.1	0.574	0.571[a]
Gender	Male	6 (40%)	7 (46.7%)	0.713	0.713[b]
	Female	9 (60%)	8 (53.3%)		
Lesion size	-	58.3 ± 40.8	54.8 ± 42.7	0.227	0.822[a]

[a] T-test; [b] Chi-square test.

Table 2
Comparison of the mean changes of the verbal performance (P-WAB-1) score within the group, and between groups in different time points.

Assessment time	Active tDCS		Sham tDCS		T- test	p-value
	Mean Score	SD	Mean Score	SD		
Baseline	18.5	12.9	28.4	11.1	2.25	0.033
After tDCS	50.4	11.9	31.2	11.9	4.41	0.0001
3 months follow up	57.9	13.3	36.5	13.4	4.33	0.0001
Trend	$F = 161.7, P \leq 0.0001$		$F = 59.3, P \leq 0.0001$			
Comparison of baseline and follow up	M.D. = −39.3 Paired T-test = 12.7 $P \leq 0.0001$		M.D. = −7.8 Paired T-test = 7.7 $P \leq 0.0001$			

*Repeated measures ANOVA; M.D.: mean difference.

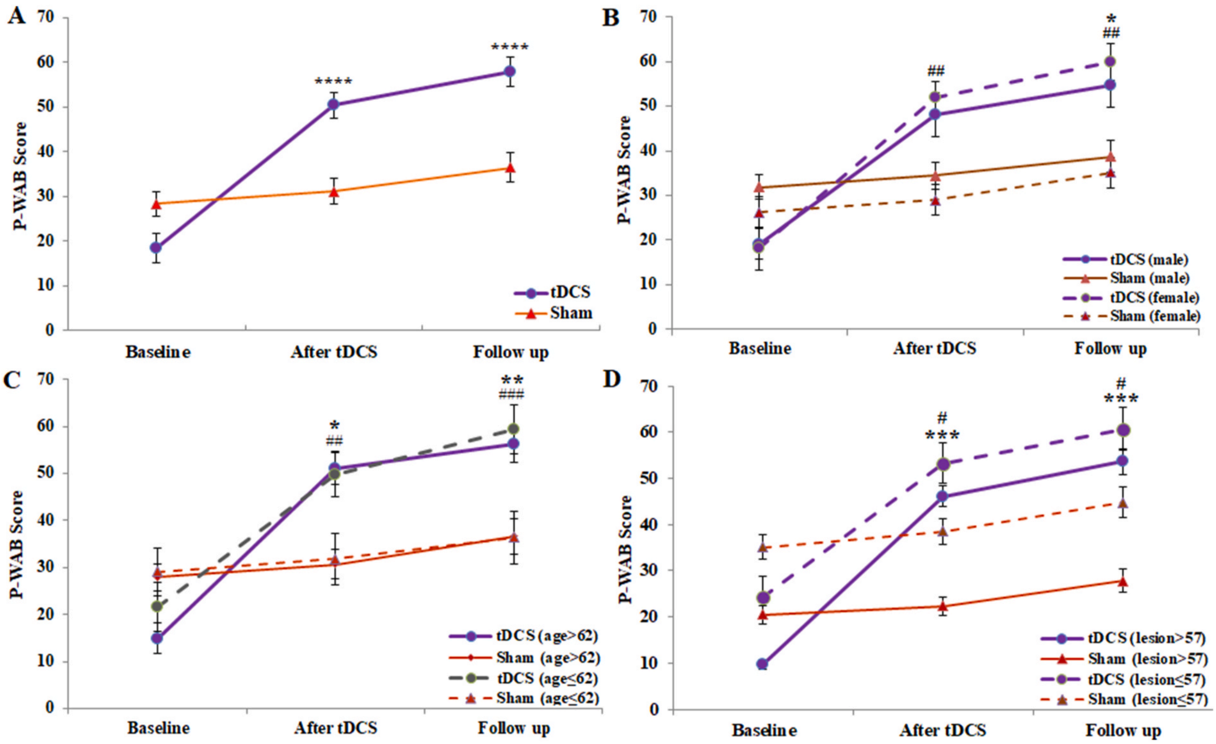

Fig. 3. The trend of changes in mean verbal performance score of patients with Broca's aphasia. Comparison of trend changes in active and sham tDCS at different time points (A). Alterations in P-WAB-1 score of patients within each group according to gender differences (B); $^{*}P \leq 0.05$ tDCS vs. sham in men; $^{##}P \leq 0.01$ tDCS vs. Sham in women. The trend of changes in the mean verbal performance score of patients within each group according to age differences (C); $^{*}P \leq 0.05$, $^{**}P \leq 0.01$ tDCS vs. sham in ages below 62 years; ##$P \leq 0.01$, ###$P \leq 0.001$ tDCS vs. Sham in ages above 62 years. Alterations in P-WAB-1 score of patients within each group according to lesion volume (D); ***$P \leq 0.001$ tDCS vs. sham in lesions wider than 57mm3; #$P \leq 0.05$, tDCS vs. Sham in lesions smaller than 57 mm^3.

higher scores immediately after tDCS and on the 3-month follow-up test (Table 3).

There was a significant increase in the P-WAB-1 score after active tDCS in both genders. Similar results were obtained using repeated measures analysis ($p < 0.0001$); within-group changes were significant in both sexes ($P < 0.001$). As depicted in Fig. 3C and D, both age groups and both lesion volume groups (based on the mean lesion size) showed similar results, three months after active tDCS according to repeated measures analysis ($p < 0.0001$) for within-group changes (Table 4).

According to the linear regression results in Table 5, intervention with tDCS is not associated with verbal performance scores independent of age, sex and lesion volume. A negative regression coefficient of −33.3 indicates that the intervention group's verbal performance changes are more than in the sham group. Age, sex, and lesion volume are not associated with patients' verbal performance outcomes.

4. Discussion

The present study results showed that the verbal performance of patients with Broca's aphasia improved after seven sessions of

Table 3
Comparison of intergroup changes according to the studied factors at baseline, after tDCS, and in the 3 months follow-up.

Variable	Class	Baseline		Statistic, P-value	After tDCS		Statistic, P-value	3 month follow up		Statistic, P-value
		Active	Sham		Active	Sham		Active	Sham	
Gender	Male	19.1 ± 9.9	31.8 ± 7.2	T = 2.7 P = 0.02	48 ± 14.1	34.5 ± 7.8	T = 2.2 P = 0.051	54.7 ± 13.8	38.7 ± 9.6	T = 2.4 P = 0.03
	Female	18.1 ± 15.2	25.4 ± 13.3	T = 1.04 P = 0.316	51.9 ± 10.9	28.3 ± 14.5	T = 3.8 P = 0.002	59.9 ± 13.1	34.2 ± 16.8	T = 3.4 P = 0.004
Age	Below 62	21.6 ± 14.6	29.1 ± 14.2	T = 0.96 P = 0.355	49.7 ± 12.9	31.9 ± 15.4	T = 2.35 P = 0.036	59.3 ± 14.4	36.4 ± 15.9	T = 2.8 P = 0.016
	Above 62	14.9 ± 10.7	27.9 ± 9.3	T = 2.5 P = 0.022	51.1 ± 11.6	30.7 ± 9.9	T = 3.7 P = 0.002	56.1 ± 12.3	36.6 ± 12.3	T = 3.06 P = 0.009
Lesion volume	Less than 57 mm	24.4 ± 13.4	35.1 ± 8.06	T = 2.1 P = 0.056	53.3 ± 12.9	38.5 ± 8.4	T = 2.8 P = 0.011	60.7 ± 13.7	44.7 ± 9.8	T = 2.7 P = 0.016
	More than 57 mm	9.7 ± 4.9	18.3 ± 5.9	T = 2.7 P = 0.012	46.06 ± 9.6	20.2 ± 6.8	T = 5.4 P < 0.001	53.6 ± 12.08	25.5 ± 8.8	T = 4.6 P < 0.001

Table 4
Comparison of changes among the groups according to the studied factors in different time points.

Variable	Class	Active tDCS			Statistic, P-value	Sham tDCS			Statistic, P-value
		Baseline	After tDCS	3 month Follow up		Baseline	After tDCS	3 month Follow up	
Gender	Male	19.1 ± 9.9	48 ± 14.1	54.7 ± 13.8	F = 47.6, P ≤ 0.001	31.8 ± 7.2	34.5 ± 7.8	38.7 ± 9.6	F = 24.9, P ≤ 0.01
	Female	18.1 ± 15.2	51.9 ± 10.9	59.9 ± 13.1	F = 117.7, P ≤ 0.0001	25.4 ± 13.3	28.3 ± 14.5	34.2 ± 16.8	F = 34.8, P ≤ 0.001
Age	Below 62	21.6 ± 14.6	49.7 ± 12.9	59.3 ± 14.4	F = 54.3, P ≤ 0.0001	29.1 ± 14.2	31.9 ± 15.4	36.4 ± 15.9	F = 26.5, P ≤ 0.01
	Above 62	14.9 ± 10.7	51.1 ± 11.6	56.1 ± 12.3	F = 142.9, P ≤ 0.0001	27.9 ± 9.3	30.7 ± 9.9	36.6 ± 12.3	F = 31.3, P ≤ 0.001
Lesion Size	Less than 57 mm	24.4 ± 13.4	53.3 ± 12.9	60.7 ± 13.7	F = 94.8, P ≤ 0.0001	35.1 ± 8.1	38.5 ± 8.4	44.7 ± 9.8	F = 63.4, P ≤ 0.0001
	More than 57 mm	9.7 ± 4.9	46.1 ± 9.6	53.6 ± 12.1	F = 71.9, P ≤ 0.0001	18.3 ± 5.9	20.2 ± 6.8	25.5 ± 8.8	F = 12.5, P ≤ 0.05

Table 5
The Results of linear regression on the effect of tDCS on verbal function after adjustment for age, gender, lesion volume.

Model	Unstandardized Coefficients		Standardized Coefficients	T statistic	P-value
	B	Std. Error	Beta		
(Constant)	74.511	14.026		5.312	0.000
tDCS	−33.035	4.099	−0.832	−8.058	0.000
Age	−0.135	0.203	−0.072	−0.666	0.512
Gender	1.888	4.361	0.047	0.433	0.669
Lesion volume	0.058	0.051	0.117	1.129	0.270

active tDCS, and this improvement remained for three months independent of age, gender, and lesion volume. Spielmann et al. presented that anodic tDCS on the left inferior frontal gyrus (IFG) had a positive effect on verbal and social communication and quality of life in patients with aphasia, which was maintained in the six months follow-up. They suggested the application of tDCS in routine aphasia recovery programs (Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2016), but the debate about the optimal electrode placement, stimulus intensity, duration, and the number of treatment sessions is still ongoing. Spielmann et al. applied 2 weeks of daily tDCS (1 mA for 20 min) combined with a word-finding task, while in the present study, just seven tDCS sessions (2 mA for 20 min) were applied without any behavioral co-therapy to evaluate the net effect of active versus sham tDCS. Shah-Basak et al. conducted a two-phase study in chronic stroke patients; they administered 4 active configurations (left/right hemisphere anode or cathode) *vs.* sham tDCS in phase 1, and patients who responded in phase1 were randomized to receive active or sham tDCS for 10 days. The results of their study showed that in phase 1 the greatest improvement was observed following cathodal stimulation of the left side; phase 2 revealed that the severity of aphasia decreased two weeks and two months after active tDCS (Shah-Basak et al., 2015).

Norise et al. exposed patients with moderate to severe aphasia to 2 mA current through 5 × 5 cm electrodes for 20 min. They concluded that at least for certain outcome measures, baseline severity is an essential factor determining the response to tDCS in patients with chronic aphasia (Norise et al., 2017). Thus, individual factors such as age, lesion size, and its relative contribution to aphasia may lead to individual variability in response to tDCS (Spielmann et al., 2016). In order to assess if the effectiveness of the treatment is affected by age or lesion size, we divided the patients into two age and two lesion size subgroups based on the approximate average age and lesion size of the participants; the results revealed that both age groups were equally meliorated after active tDCS. Whereas Tan et al. presented that active tDCS on the left prefrontal cortex had less effectiveness in elder participants in response selection training (Tan, Filmer, & Dux, 2021).

In the same way, the current tDCS protocol had the same influence on wider and smaller lesion sizes. Studies have shown that the combined application of anodal tDCS on the lesioned area and cathodal tDCS on the opposite side of the lesion have longer-lasting effects in patients with moderate to severe chronic stroke (Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Lindenberg, Zhu, & Schlaug, 2012). Similarly, anodal tDCS was applied to the lesion-side cortex and cathodic tDCS to the opposite side in the present study. Wu et al. assessed the effect of anodal tDCS on the left side of the posterior region of the Sylvian groove on image naming and cortical excitability in aphasic patients. The results showed that the combination of tDCS and speech therapy improves patients' performance. TDCS does not affect just the areas directly stimulated by the electrode but also areas of the brain that are functionally related (Wu et al., 2015). Lee et al. conducted a dual tDCS cross-over study on chronic stroke patients with aphasia. Dual tDCS was performed in two modes: 1) using anodal tDCS on the left IFG (LIFG) and cathodic tDCS on the left buccinators muscle, 2) cathodic tDCS on the right IFG and anodal tDCS on the right buccinators muscle. Dual tDCS had a more significant effect on patients' verbal performance (Lee, Cheon, Yoon, Chang, & Kim, 2013).

The results of this study indicate that 86.6% of patients (13 out of 15 cases in the active group) showed general improvement in all categories. The analysis of verbal performance in different P-WAB-1 categories revealed the most improvement in auditory comprehension and naming ability. Most of the previous studies implicated anodal tDCS in Broca's area (LIFG) (Baker et al., 2010; Campana, Caltagirone, & Marangolo, 2015; P.; Marangolo, Fiori, Calpagnano, et al., 2013) or left Wernicke's region (superior temporal gyrus) (Marangolo et al., 2014); many of them combined brain stimulation with repetition or naming tasks in order to boost the Broca's neural function (Marangolo, Fiori, Di Paola et al., 2013). As reviewed by Biou et al., these studies were mainly conducted on patients in the chronic phase of stroke (Biou et al., 2019); Fiori et al., reported that five sessions of anodal tDCS on Wernicke's area combined with a picture-naming task resulted in an improvement in naming accuracy with shorter naming latencies in chronic stroke patients, which persisted for three weeks (Fiori et al., 2011). Pestalozzi et al., evaluated the effect of 2 mA anodal tDCS on left DLPFC combined with picture naming and repetition tasks. They observed improvement in verbal fluency but not in word repetition (Pestalozzi et al., 2018). In the present study, seven sessions of bi-temporal tDCS were applied on both hemispheres; the anode electrode was placed on the left DLPFC (F3 zone), whereas the cathode was placed on the right side (F4), without any additional speech therapy. The results indicate 37.3% improvement in auditory comprehension, 34% in naming accuracy, and 32.6% in repetition task, which endured for 3 months. The main differences in this study were the period of intervention (between 10 and 20 days after stroke onset) in the sub-acute phase of stroke and simultaneous excitation in the lesioned hemisphere (with the anodal electrode) and inhibition of contralateral DLPFC with cathodic tDCS, which could suppress the adverse effects of interhemispheric inhibition (Boddington & Reynolds, 2017). You et al. applied 10 sessions of either anodal tDCS on the left Wernicke's area or cathodal tDCS on the right side in the sub-acute stage of stroke. They reported improved verbal comprehension in patients receiving cathodal stimulation (You et al., 2011). Spielmann et al., did not observe any significant difference after 5 sessions of anodal stimulation on LIFG in sub-acute stroke patients (Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018).

Besides, sex did not affect the response to intervention. In contrast to this result, Panagiotis et al., examined the effect of gender on tDCS outcome on naming ability in patients with aphasic stroke. They found that the application of tDCS to the IFG region was significantly more effective in female patients (Karagounis Panagiotis, 2017). Martin et al. also revealed the effect of gender on the results of dorsomedial prefrontal cortex tDCS treatment on memory and visual function of patients (Martin, Huang, Hunold, & Meinzer, 2017). Mezger et al., using magnetic resonance spectroscopy (MRS), stated a significantly more substantial glutamate reduction after active tDCS compared to sham stimulation in female participants but not in male participants (Mezger et al., 2021). In the present study, we observed a between-group difference in language performance at baseline, which could be considered a limitation of this study. However, since patients in the active tDCS group had a lower P-WAB-1 score than patients in the sham group at the beginning of the study, this further reinforces the effectiveness of the tDCS protocol.

5. Conclusion

In conclusion, the present study's evidence suggests that bi-hemispheric tDCS on F3 and F4 regions in patients with post-stroke Broca's aphasia in the subacute phase is an effective procedure in improving the verbal function independent of age, gender, and lesion volume.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the ***Journal of Neurolinguistics***.

Authorship contributions

Conception and design of study: A. Saberi, K. Rohampour, K. Ezzati, S. Andalib; Acquisition of data: S. Yekta, S. Ghorbani Shirkouhi; Analysis and/or interpretation of data: S. Yekta, S. Ahmadi Gooraji, S. Andalib.

Drafting the manuscript: S. Yekta, K. Rohampour, A. Saberi, S. Andalib; Revising the manuscript critically for important intellectual content:

K. Ezzati, S. Ghorbani Shirkouhi, S.Ahmadi Gooraji.

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