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Original Article

Comparison of the Effect of Four Transcranial Direct Current Stimulation Configurations on Picture-Naming Improvement in Non-Fluent Aphasia: A Randomized Clinical Trial

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Abstract

Background: Anomia is a language disorder that negatively affects communication abilities in people with aphasia (PWA). We aimed to compare the effect of transcranial direct current stimulation (tDCS) over the left and right inferior frontal gyrus (IFG) and superior temporal gyrus (STG) on the picture-naming accuracy and reaction time in PWA.

Methods: A randomized, single-blind, sham-controlled crossover trial was conducted in 2021 at Mobasher Kashani Clinic, Hamadan, Iran. Sixteen patients received both five days of real-tDCS (1 mA for 20 minutes) and five days of sham-tDCS with a seven-day washout period in between. Using the Persian aphasia naming test, picture-naming accuracy and reaction time on 50 images were assessed at baseline, real-tDCS, and sham-tDCS stages. The data were analyzed using STATA software, version 11.0. P<0.05 was considered statistically significant.

Results: Sixteen non-fluent PWA participated in the study. Of all patients, 64% benefited from tDCS over the STG and 18% over the IFG. The results showed that real-tDCS had a significant effect on the picture-naming accuracy (P=0.003) and the Persian-Western aphasia battery-one score (P=0.01), whereas sham-tDCS had no noticeable effects. Both the real- and sham-tDCS had no significant effect on the reaction time (P=0.28).

Conclusion: Five sessions of individualized tDCS protocol (1 mA for 20 minutes) were adequate to improve picture-naming accuracy in patients with chronic aphasia.

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Keywords ● Transcranial direct current stimulation ● Aphasia ● Anomia ● Reaction time

What's Known

- Transcranial direct current stimulation (tDCS) is a non-invasive and safe method to stimulate the brain.
- Depending on the targeted areas and polarity of stimulation, tDCS is an effective intervention method to improve post-stroke language impairment in aphasic individuals.

What's New

- To the best of our knowledge, for the first time, the effect of an individualized tDCS protocol to improve anomia in aphasic patients were investigated.
- Of the four tDCS configurations, the superior temporal gyrus is the optimal location to stimulate the brain.

Introduction

Word retrieval impairment (also known as anomia) is the most frequent symptom in people with aphasia (PWA).[1] In recent years, transcranial direct current stimulation (tDCS) has been utilized as an adjuvant therapy to improve the motor and language recovery process in these patients.[2-6] tDCS is a non-invasive cortical neuromodulation process that alters spontaneous neuronal excitability through tonic depolarization or hyperpolarization of the resting membrane potential.[7] In general, anodal tDCS is shown to increase cortical excitability, whereas cathodal stimulation has an inhibitory effect.[8]

Over the past 10 years, various studies have investigated tDCS as a technique to improve impaired naming abilities in individuals with post-stroke aphasia. Several studies suggested the efficacy of anodal tDCS over the left regions of the brain, including Broca's[2, 4, 9, 10] and Wernicke's[9, 11, 12] areas to improve naming abilities. However, Kang and colleagues suggested that cathodal stimulation over the right healthy Broca's homolog area can improve picture-naming ability in post-stroke aphasic patients.[13] Spielmann and colleagues reported that stimulation of the left inferior frontal gyrus (IFG) is the optimal configuration for half of the PWA.[14] In another study, Silva and colleagues observed better performance in naming ability after simultaneous anodal and cathodal tDCS of the left Broca's area and its homolog area in the right-hemisphere in PWA.[15]

Based on the post-lesion recovery process, brain reorganization proceeds in three phases, namely (i) a significantly reduced activation of the remaining left language areas in the acute phase (ii) recruitment of homolog language brain areas, and (iii) normalization of activation of the left-hemisphere language.[16] Factors affecting language recovery by the two hemispheres are the lesion site and size, recovery phases, and individualized pattern of language lateralization.[17] Therefore, there is a quite large variation in brain reorganization upon the occurrence of a lesion. Given the various ways of recovering from aphasia, it is possible that reducing the inhibition of the right-hemisphere by cathodal stimulation is more beneficial for some PWA, while anodal stimulation of the perilesional areas is better for others. It seems that excitatory stimulation of the left IFG or superior temporal gyrus (STG) and inhibitory stimulation of the right IFG or STG are the most widely used tDCS protocols to recover naming abilities in PWA.[5, 10-12, 14, 18, 19]

Considering the complexity of brain reorganization after stroke, for the first time, Basat and colleagues attempted to develop an efficient protocol for individualized tDCS to treat naming deficits in seven patients with chronic aphasia. They assessed the best stimulation area (Broca or Wernicke), the best side (left or right hemisphere), and the best type of stimulation (anodal or cathodal). Despite major efforts, they concluded that there was great variability in stimulation types and locations in their patients, to the extent that only two pairs of patients benefited from the same stimulation type.[20]

In the present study, for the first time, alternative individualized tDCS protocols were examined to determine the optimal type of stimulation and the best target site. Four different configurations were used and compared, namely anodal-tDCS over the left STG, anodal-tDCS over the left IFG, cathodal-tDCS over the right STG, and cathodal-tDCS over the right IFG. In addition, the effect of tDCS on the brain regions related to picture-naming accuracy and reaction time was evaluated in PWA.

Patients and Methods

A randomized, single-blind, sham-controlled crossover trial[21] was conducted in 2021 at Mobasher Kashani Clinic, Hamadan, Iran. The study was approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (code: IR.UMSHA.REC.1399.652) and registered on the Iranian Registry of Clinical Trials (code: IRCT20160509027820N2). Written informed consent was obtained from all participants. The participants were selected using convenience sampling, and the sample size was calculated according to the below formula.[22]

$$n = \frac{\sigma_d^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2}{2\Delta^2}$$

$Z_{1-\beta}$ and $Z_{1-\alpha/2}$ are "power" and "type I error", respectively. If the true difference between treatments is 10 units, the probability of detecting a treatment difference at a two-sided 0.05 significance level is 91%. This is based on the assumption that the standard deviation of the within-patient variable is eight.[23] Accordingly, a sample size of 16 was calculated. Due to possible loss to follow-up, a total of 22 patients were enrolled in the study, of which 16 completed the treatment.

The inclusion criteria were Persian language proficiency, right-handedness based on the results of the Edinburgh Handedness Inventory,[24] and a single left-sided hemispheric stroke at least six months prior to the study. The exclusion criteria were global aphasia, severe apraxia of speech, a history of psychiatric disease, dysarthria, current use of antipsychotic drugs, wearing of a pacemaker, a seizure within the previous 36 months, and a score of >75% in the Persian aphasia picture-naming test.

Experimental Procedure: Phase I

At the baseline, picture-naming accuracy and reaction time were determined. Each patient received four stimulations (1 mA for 20 min) per day with four types of configurations, namely anodal-tDCS above left IFG, cathodal-tDCS above right IFG, anodal-tDCS above left STG, and cathodal-tDCS above right STG. After each stimulation, the patients were requested to name a block of 30 images.

Experimental Procedure: Phase II

After determining the optimal stimulation protocol for each PWA, patients entered the second phase. The patients, in the order of enrollment in the study, were given a random number based on which each patient was assigned to a real- or sham-tDCS session. Those with odd numbers (n=8) received real-tDCS over five consecutive days, and after seven days of rest (to eliminate the carryover effect) they received sham-tDCS in the same manner. Patients with even numbers (n=8) followed the same stimulations but in reverse. All patients were blinded to the type of tDCS.

After each stimulation session (real or sham), picture-naming accuracy and reaction time, as well as the score of the Persian-Western Aphasia Battery-1 (P-WAB-1) questionnaire, were assessed. Stimulation was delivered through a pair of surface-soaked sponge electrodes of 5×7 cm using a current stimulator (ActivaDose® II Iontophoresis Delivery Unit, USA). The active electrode was positioned above the neural location that showed the most significant improvement in picture-naming. The left IFG was positioned at the intersection of T3-Fz and F7-Cz. The right IFG was positioned at the crossing of T4-Fz and F8-Cz. The left and right STGs were determined as T3 and T4, respectively, using the international 10-20 system (figure 1).[25] The reference electrode was positioned above the contralateral supra-orbital area. To examine any potential placebo effect, five sham therapy sessions were also carried out. However, in the sham sessions, the stimulator was switched off after 30 sec. The study design is depicted in figure 2.

Measurement Instrument

The severity of aphasia was assessed with the P-WAB-1 questionnaire using the standard paper-and-pencil test. The questionnaire includes six sections, namely spontaneous speech content, fluency of spontaneous speech, auditory comprehension, sequential commands, repetition, and naming. The maximum score for each section is 10 points. Using the aphasia

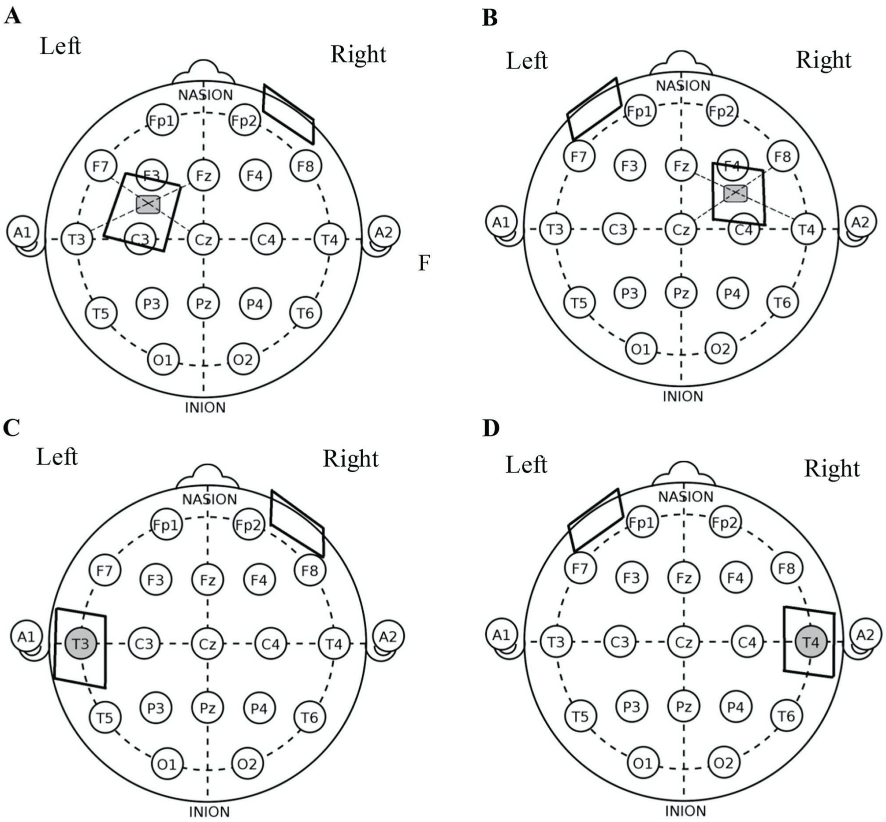

Figure 1: This figure shows the electrode montage for tDCS stimulation. The tDCS was applied by a pair of surface-soaked sponge electrodes of 5×7 cm. To stimulate the left and right IFG and STG regions, four different electrode stimulation positions were applied using the 10-20 EEG system. The left IFG was defined as the crossing point between T3-Fz and F7-Cz (A). The right IFG was defined as the crossing point between T4-Fz and F8-Cz (B). The left STG was defined as T3 (C), and the right STG was identified as T4 (D). In all positions, the reference electrode was placed over the contralateral supra-orbital area.

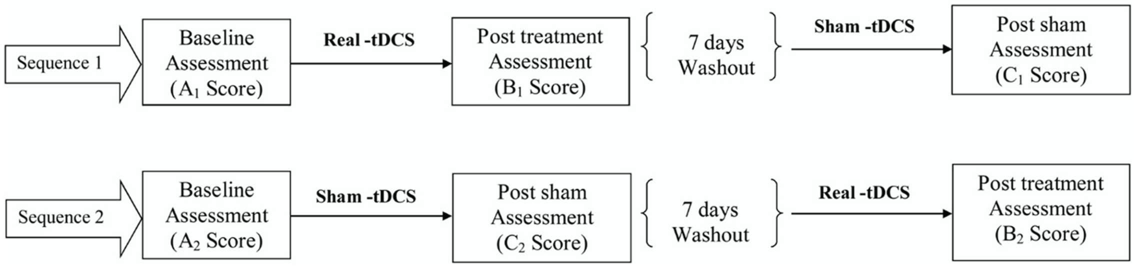

Figure 2: This chart shows the crossover design of the study. Patients were randomly assigned to two sequences. The first sequence started with real-tDCS followed by sham-tDCS, whereas the second sequence was applied in reverse.

quotient (AQ), a summary score was deduced, based on which the PWA was classified into four distinct groups of severity.[26] The Persian aphasia picture-naming test with 50 normalized black and white pictures was used to assess naming abilities. In addition, 120 images of names were used to measure the frequency of use, the number of syllables, visual complexity, age of acquisition, and length of word.[27] All images were of the same size (height=9 cm, width=10.05 cm) and displayed in the center of a personal computer screen for 10 sec with one sec interstimulus interval using the DMDX software, version 4.0 (University of Arizona, USA). A fixation point was displayed in the center of the screen together with a 120 ms beep to sequence the images. The patients were asked to name the displayed images as soon as possible, after which correct and incorrect responses received a score of one or zero, respectively.

Statistical Analysis

Data were analyzed using STATA software, version 11.0 (StataCorp LLC, USA). Analysis of variance (ANOVA) for a 2×2 crossover study was conducted to determine the effect of real-tDCS compared to sham-tDCS in terms of the period effect and carryover effect. First, the data was reshaped using the syntax “pkshape id sequence period 1 period 2 [period list], [options]”. Then, the syntax “pkcross outcome [if] [in], [options]” was used to analyze the crossover design. For each dependent variable, the “treatment effect”, “carryover effect”, and “period effect” were calculated. The Kolmogorov-Smirnov test was used to examine the normal distribution of all variables. P<0.05 was considered statistically significant.

Results

Of the 22 eligible PWA, six patients were excluded during phase I of the study, and the remaining 16 were assigned to real- and sham-tDCS groups (figure 3). The demographic characteristics of the patients are presented in table 1. Based on the Persian aphasia naming test scores, all participants had impairment in naming ability. Table 2 presents the language profiles of the participants, including the P-WAB-1 score, AQ score, and severity of aphasia. The mean AQ score of patients with mild to severe aphasia was 59.22±3.58 (range=39.10-85). The application of tDCS was well-tolerated by all participants, and no adverse effects were observed.

Determination of Stimulation Location and Type

To determine the optimal stimulation location and type for each patient, each tDCS configuration was calculated during pre-treatment assessment sessions. The normalized improvement value for each participant was computed by dividing the difference in picture-naming scores (post- minus pre-tDCS total accuracy) by the individual standard deviation of items. These levels were then categorized into four blocks. Compared with baseline, post-tDCS naming ability scores improved in all patients, except for three participants. The standard deviation of the normalized improvement values ranged from 0.38 to 1.62 (table 1). Three combinations of stimulation types and sites were applied. Seven patients gained the greatest benefits from the cathodal-tDCS over the right STG, in six patients the optimal outcome was achieved with the anodal-tDCS over the left STG, and in three patients this was achieved with the anodal-tDCS over the left IFG. Due to low or negative normalized improvement values, we could not identify an optimal stimulation condition for four patients (patient numbers: P4, P5, P17, and P22). Therefore, these patients were excluded from phase II of the study.

Comparison between Real-tDCS and Sham-tDCS Results

To determine the response accuracy and reaction time for each patient, the difference between the pre- and post-stimulation Persian aphasia picture-naming test scores was calculated (table 3). The results of ANOVA for a 2×2 crossover study showed that the period

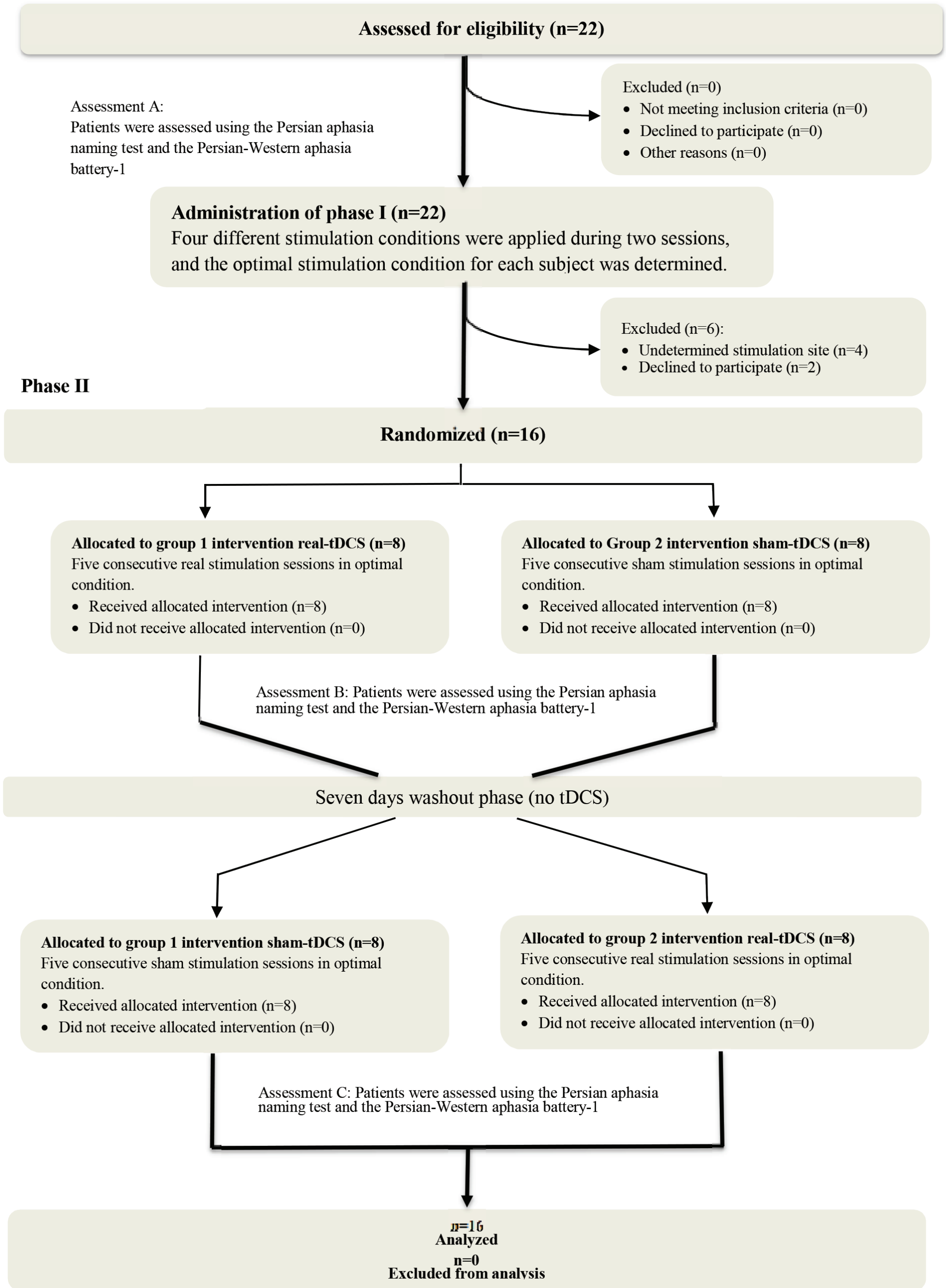

Figure 3: CONSORT diagram shows the process of patient recruitment and allocation.

effect (F=2.22, P=0.155), and carryover effect (F=3.98, P=0.063) had no significant effect on the reaction time for picture-naming (table 4). Moreover, in terms of the picture-naming accuracy, the period effect (F=3.22, P=0.090) and carryover effect (F=0.97, P=0.339) were not significant. Except for two patients (P9 and P16) who managed to significantly reduce the reaction time, other participants showed no significant post-real-tDCS improvement in picture-naming reaction time. The latency in those two patients significantly improved both after real- and sham-tDCS. However, we believe the improvement in the picture-naming reaction time was not because of the tDCS protocol, but rather due to increased familiarity with the test items. Therefore, the difference can be attributed to the post-real-tDCS treatment. Furthermore, the intervention had a significant effect on the accuracy of picture-naming (F=11.39, P=0.003), but had no significant effect on picture-naming reaction time (F=1.21, P=0.288). Moreover, the period effect (F=0.32, P=0.578) and carryover effect (F=0.38, P=0.547) were not significant.

Table 1: Demographic characteristics of the patient and the type and site of optimal stimulation

Patient	Age (years)	Sex	Years of education	Post-stroke duration (months)	Loci of the lesion (left hemisphere)	Type of lesion	Type of stimulation	Location of stimulation	Normalized improvement
P1	59	F	5	41	Fronto-parietal and left basal ganglia	Ischemic	Cathodal	R-STG	1.49
P2	54	M	4	16	Temporo-occipital	Ischemic	Anodal	L-STG	0.44
P3	57	M	7	7	Temporo-parietal	Hemorrhagic	Cathodal	R-STG	0.46
P4	52	M	12	32	Temporal and basal ganglia	Ischemic	Indeterminate		-0.48
P5	32	F	16	21	Fronto-temporo-parietal	Ischemic	Indeterminate		0.25
P6	55	M	12	48	Temporo-parietal	Ischemic	Anodal	L-IFG	0.38
P7	42	F	12	38	Fronto-temporal	Ischemic	Cathodal	R-STG	1.15
P8	67	M	8	9	Fronto-temporal	Ischemic	Anodal	L-IFG	1.11
P9	69	M	8	6	Basal ganglia and cerebellum	Ischemic	Cathodal	R-STG	0.41
P10	58	M	8	14	Fronto-parietal	Ischemic	Anodal	L-IFG	0.68
P11	58	M	16	69	Basal ganglia, left putamen	Hemorrhagic	Cathodal	R-STG	1.20
P12	56	M	12	108	Fronto-temporo-parietal	Ischemic	Anodal	L-STG	1.33
P13	46	F	16	38	Frontal	Ischemic	Anodal	L-STG	1.20
P14	56	M	12	39	Temporal	Ischemic	Anodal	L-STG	0.83
P15	56	M	16	122	Temporo-parietal	Ischemic	Anodal	L-STG	1.43
P16	59	M	16	7	Frontal	Ischemic	Cathodal	R-STG	1.05
P17	49	M	12	11	Frontal, para, and periventricular, centrum semioval	Ischemic	Indeterminate		-0.23
P18	43	F	19	11	Temporo-parietal	Ischemic	Cathodal	R-STG	0.74
P19	63	F	12	6	Frontal and parieto-occipital	Hemorrhagic	Anodal	L-STG	1.62
P20	49	M	12	6	Fronto-parietal	Ischemic	Anodal	L-STG	0.98
P21	57	F	14	7	Fronto-temporal	Ischemic	Anodal	L-STG	1.39
P22	61	M	8	12	Temporo-parieto-occipital	Hemorrhagic	Indeterminate		-0.12
Mean ±SD	54.45 ±8.45	-	11.68 ±3.98	30.36 ±32.41	-			-	0.83 ±0.52

F: Female; M: Male; R-STG: Right superior temporal gyrus; L-STG: Left superior temporal gyrus; R-IFG: Right inferior frontal gyrus; L-IFG: Left inferior frontal gyrus

However, the effect of treatment on the P-WAB-1 score (F=7.87, P=0.011) was significant.

Discussion

To the best of our knowledge, for the first time, we determined which stimulation electrode montage (i.e., anodal left STG, cathodal right STG, anodal left IFG, and cathodal right IFG) is most effective for each patient. The data suggested that PWA most benefited from the cathodal-tDCS over the right STG and anodal-tDCS over the left STG configurations. Furthermore, five sessions of tDCS treatment were adequate to significantly

Table 2: Language profile of the patients

Patient	Persian-Western Aphasia Battery-1 (P-WAB-1)							
	Content	Fluency	Auditory comprehension	Sequential commands	Repetition	Naming	AQ	Aphasia severity
P1	2	1	7	7	3	7.5	45	Severe
P2	6.5	3	9	4	2	3.5	46.5	Severe
P3	8	4	10	10	8	8	80	Mild
P4	2	0	10	10	2	2.5	44.16	Severe
P5	2.5	1	8	7.5	3.5	1	39.1	Severe
P6	7	7	8	8	5.5	2	62.5	Moderate
P7	7.5	2	9	6	7	5.5	61.6	Moderate
P8	6.5	2	10	9.5	2	2.5	54.16	Moderate
P9	4	1	7	6	9.5	7	57.5	Moderate
P10	3.5	3	9	5	10	7.5	63.3	Moderate
P11	2	0	8	6	3.5	2	32.5	Severe
P12	6	1	9	9.5	9	9	72.5	Moderate
P13	8	5	8	6	7	7	68.33	Moderate
P14	5.5	4	8	8	3.5	7.5	60.83	Moderate
P15	6	2	9	10	9	8	73.3	Moderate
P16	2	5	9	9	2.5	2	47.2	Severe
P17	7	3	9	9	7	6.5	69.16	Moderate
P18	6.5	6	7	8	6.5	7	68.33	Moderate
P19	2	1	8	7.5	8	5	52.5	Moderate
P20	4.5	2	9	6	4.5	3.5	49.16	Severe
P21	5	3	10	8	5.5	5.5	61.66	Moderate
P22	3	0	7	8	2	2	36.66	Severe

AQ: Aphasia quotient (maximum score=100)

Table 3: The Persian aphasia picture-naming test score for each patient pre- and post-stimulation (accuracy and reaction time)

Patient code	Initial intervention	Real-tDCS						Sham-tDCS					
		Number of correct responses			Reaction time (second)			Number of correct responses			Reaction time (second)		
		Baseline	Post	Δ	Baseline	Post	Δ	Baseline	Post	Δ	Baseline	Post	Δ
P1	Real-tDCS	17	28	11	4.13	3.63	-0.5	17	22	5	4.13	5.79	1.66
P2	Sham-tDCS	22	32	10	2.43	2.22	-0.21	22	25	3	2.43	3.21	0.78
P3	Real-tDCS	29	38	9	2.63	2.82	-0.19	29	32	3	2.63	4.06	1.43
P6	Sham-tDCS	8	12	5	2.74	4.17	1.43	8	9	2	2.74	2.14	-0.6
P7	Real-tDCS	19	31	12	4.45	3.97	-0.48	19	29	10	4.45	4.16	-0.29
P8	Sham-tDCS	29	41	12	1.82	1.21	-0.61	29	28	-1	1.82	2.06	0.24
P9	Real-tDCS	14	31	17	4.71	1.90	-2.81	14	21	7	4.71	2.35	-2.36
P10	Sham-tDCS	37	43	6	2.27	1.25	-1.02	37	35	-2	2.27	1.77	-0.5
P11	Real-tDCS	10	21	11	5.35	4.12	-1.23	10	25	15	5.35	5.11	-0.24
P12	Sham-tDCS	34	43	12	1.78	1.85	0.07	34	37	3	1.78	2.08	0.3
P13	Real-tDCS	36	43	7	2.43	2.95	0.52	36	38	2	2.43	2.14	-0.29
P14	Sham-tDCS	22	31	9	3.53	3.91	0.38	22	24	2	3.53	3.01	-0.52
P15	Real-tDCS	33	45	12	1.62	1.93	0.31	33	39	6	1.62	1.69	0.07
P16	Sham-tDCS	13	18	5	3.44	1.97	-1.47	13	10	-3	3.44	1.41	-2.03
P18	Sham-tDCS	24	36	12	1.69	1.32	-0.37	24	27	3	1.69	1.89	0.2
P19	Real-tDCS	5	21	16	2.07	2.11	0.04	5	13	8	2.07	2.93	0.86

tDCS: Transcranial direct current stimulation; Δ=Delta (post-tDCS vs. pre-tDCS)

improve patients' ability in terms of language and picture-naming accuracy. However, the sessions did not improve their reaction time. Sham stimulation did not have any effect. Given that cathodal-tDCS has an inhibitory effect, stimulation over the right STG might lead to improved performance of the left STG. In other words, it can be a potential mechanism by which cathodal right STG stimulation (or direct improvement of the left STF) may improve naming ability.

Object naming is a process that involves different linguistic functions. Studies showed that naming impairment is related to loci around the STG areas, including the left anterior temporal, left temporal pole, and left posterior temporal

Table 4: Analysis of Variance (ANOVA) for 2×2 crossover study in accuracy and reaction time of picture-naming, and Persian Western Aphasia Battery-1

Source of variation	Accuracy		RT		P-WAB-1	
	F	P value	F	P value	F	P value
Inter-subject						
Sequence effect	0.97	0.339	3.98	0.063	0.38	0.545
Intra-subject						
Treatment effect	11.39	0.003*	1.21	0.288	7.87	0.011*
Period effect	3.22	0.090	2.22	0.155	0.32	0.578

RT: Reaction time; P-WAB-1: Persian-Western aphasia battery-1; *ANOVA test was used to compare the variables between the inter-subject and intra-subject. P<0.05 was considered statistically significant.

regions, which lead to impaired naming of specific objects such as animals, persons, and tools.[28, 29] Therefore, a stimulation protocol for the activation of the left STG is recommended to improve naming ability in PWA.

The results of the present study showed that five consecutive tDCS sessions significantly improved picture-naming accuracy among PWA, whereas sham stimulation had no significant effect. However, no statistical difference was observed between the real-tDCS and sham-tDCS in terms of picture-naming reaction time. In line with our results, Volpato and colleagues reported that the reaction time in the sham group did not differ significantly from the tDCS group.[10] In contrast, Fridriksson and colleagues reported that anodal-tDCS during language therapy reduced picture-naming reaction time in patients with fluent aphasia.[23] These differences could be due to patients with different types of aphasia.

We found that optimal protocols for individualized tDCS improved the AQ score in the P-WAB-1 test. In all patients, the AQ score between pre- and post-tDCS increased by an average of 12 points and reduced the severity of aphasia. In some patients, it even reduced the severity of aphasia from severe to moderate. Two studies reported improvements in the language abilities of aphasic patients following anodal-tDCS over the left perisylvian region and cathodal-tDCS over the right IFG.[5, 12] These findings are in line with the results of our individualized protocols where some patients benefited from anodal-tDCS over the left IFG or left STG, and others from cathodal-tDCS over the right IFG or right STG. This may not only be due to the interaction between the brain neural networks responsible for language in the perisylvian area (e.g., two dorsal and two ventral pathways) but also interactions with other networks (e.g., the attentional networks).[30, 31]

As the main limitation of the study, because of the small sample size and variety of lesions, it was not possible to classify patients based on the loci of lesions. The development of an optimal protocol according to the loci of lesions is useful for clinical use. Another limitation was related to the lack of data functional imaging in pre-and post-stimulation. Such data give valuable insights into the specific brain networks involved in lexical retrieval following a stroke.

Conclusion

Cathodal- and anodal-tDCS over the STG were the most effective configurations in our aphasic patients. Five sessions of individualized tDCS protocol (1 mA for 20 minutes) are adequate to improve naming accuracy in patients with chronic aphasia. Our findings significantly contribute to the clinical application of tDCS as a potential tool to improve post-stroke language abilities. Future studies are required to investigate the effectiveness of dual-hemisphere stimulation, such as simultaneous cathodal-tDCS over the right STG and anodal-tDCS over the left STG (bilateral bipolar balanced montage) to further improve post-stroke language recovery.

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Authors' Contribution

B.R, A.KhB, F.Y, M.M: Study concept and design, data gathering and interpretation, drafing and revising the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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