

## No effects of anodal transcranial direct stimulation on language abilities in early rehabilitation of post-stroke aphasic patients

### *Brak wpływu anodowej przezczaszkowej stymulacji prądem stałym na funkcje językowe u chorych z afazją poudarową będących we wczesnym okresie neurorehabilitacji*

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#### Abstract

**Background and purpose:** Recent research suggests that an increased level of stroke-affected left hemisphere cortical (especially frontal) excitability is associated with better language improvement in aphasic patients. Anodal transcranial direct current stimulation (A-tDCS), increasing cortical activity, may facilitate perilesional left hemisphere recruitment to subservise language processing and enhance effects of behavioural therapy. The aim of the study (randomized, double-blind, sham-controlled) was to evaluate the effectiveness of repeated A-tDCS over Broca area as a strategy to enhance aphasia recovery during early post-stroke rehabilitation.

**Material and methods:** Thirty-seven participants with moderate or severe aphasia were randomized to receive 15 consecutive daily sessions of A-tDCS (1 mA, 10 min; experimental group,  $n = 18$ ) or sham stimulation (1 mA, 25 s; control group,  $n = 19$ ) followed by language therapy. Effects of tDCS were assessed using the Boston Diagnostic Aphasia Examination, performed before and after the rehabilitation, and three months later.

**Results:** The results did not confirm a positive impact of repeated A-tDCS, preceding language therapy, on language abilities in our patients. Although both groups improved after the therapy, there were no statistically significant differences between groups in either short-term or long-term tDCS effects. Effect sizes for the experimental group, at post-treatment

#### Streszczenie

**Wstęp i cel pracy:** Wyniki przeprowadzonych badań sugerują, że wzrost poziomu wzbudzenia korowego (szczególnie okolic czołowych) w uszkodzonej w wyniku udaru lewej półkuli mózgu wiąże się z większą poprawą funkcji językowych u chorych z afazją. Anodowa przezczaszkowa stymulacja prądem stałym (*anodal transcranial direct current stimulation – A-tDCS*) może, poprzez zwiększanie poziomu aktywacji korowej, wspomagać proces włączania się lewo-półkulowych okolic wokół ogniska uszkodzenia w przetwarzanie językowe i wzmacniać efekty terapii behawioralnej. Celem badania (z randomizacją, przeprowadzonego metodą podwójnie ślepej próby, z grupą kontrolną poddaną pozorowanej stymulacji) była ocena efektywności powtarzanej A-tDCS podawanej nad okolicą Broki jako strategii wspomagającej zdrowienie z afazji we wczesnym etapie rehabilitacji poudarowej.

**Materiał i metody:** Trzydzieści siedem osób z umiarkowaną bądź znaczną afazją otrzymało kolejno 15 codziennych sesji A-tDCS (1 mA, 10 min; grupa eksperymentalna,  $n = 18$ ) lub stymulacji pozorowanej (1 mA, 25 s; grupa kontrolna,  $n = 19$ ), po których następował trening funkcji językowych. Efekty funkcjonalne zastosowania A-tDCS oceniono przy użyciu Bostońskiego Testu do Diagnostyki Afazji, wykonywanego przed rozpoczęciem rehabilitacji, bezpośrednio po rehabilitacji i 3 miesiące od jej zakończenia.

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and the 3-month follow-up, were slightly higher than in controls but insufficient to infer any beneficial influence of the applied intervention.

**Conclusions:** The findings do not support A-tDCS functional benefits during early rehabilitation of post-stroke aphasia. Further research is needed to explore the effectiveness of this kind of neuromodulation.

**Key words:** aphasia, stroke, transcranial direct current stimulation.

**Wyniki:** Nie potwierdzono pozytywnego wpływu wielokrotnej A-tDCS, poprzedzającej trening behawioralny, na funkcje językowe u badanych pacjentów. W obu grupach stwierdzano poprawę po terapii, jednak nie odnotowano istotnych statystycznie różnic międzygrupowych w krótko- i długoterminowych efektach tDCS. Wielkości efektów w grupie eksperymentalnej po terapii i 3 miesiące później były nieco większe niż w kontrolnej, jednak zbyt małe, aby wnioskować o korzystnym wpływie zastosowanej interwencji.

**Wnioski:** Badanie nie potwierdziło funkcjonalnych korzyści A-tDCS we wczesnej rehabilitacji poudarowej. Potrzebne są dalsze badania nad potencjalną efektywnością omawianej formy neuromodulacji.

**Słowa kluczowe:** afazja, udar, przezczaszkowa stymulacja prądem stałym.

## Introduction

Aphasia, an impairment in the ability to express and/or understand language, is one of the major sources of disability due to brain injury, commonly observed after left hemisphere stroke. Most of the natural and therapy-facilitated recovery from aphasia occurs during the first six months after stroke, although significant language improvements have been described up to 18 months [1] or even several years post onset [2]. However, affected individuals often experience incomplete recovery despite intense behavioural language therapy after the acute stroke phase [3]. Because of high prevalence of aphasia and its serious consequences for the patient's life there is a pressing need for more research concerning effective therapies.

Transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory technique, is a potentially promising tool for enhancing aphasia recovery through inducing or boosting neuroplastic changes in brain activity [4-6]. According to the interhemispheric interactions model, after hemispheric stroke there are bihemispheric brain activity changes attributed to shifts in inhibitory and excitatory influences between both brain hemispheres. In the case of left hemisphere stroke, a pathologically increased excitability in the undamaged right hemisphere is observed (the effect of releasing the non-lesioned hemisphere from inhibition originating in the lesioned hemisphere) with accompanying decreased excitability in the stroke-affected left hemisphere (the effect of excessive transcallosal inhibition from the over-activated non-lesioned to the lesioned hemisphere, which is hypoactive primarily because of injury). Reviews that

include imaging studies concerning post-stroke motor [4,7,8] and language deficits [5,9,10] confirm that interhemispheric imbalance in activity may enhance functional disability, and hamper recovery, while early reactivation of the perilesional cortex in the dominant (for disrupted functions) hemisphere is generally associated with better behavioural outcome. In this context, tDCS which delivers a weak polarizing electric current may promote restoration of a more adaptive equilibrium in imbalanced neuronal networks by either increasing spontaneous activity in the damaged hemisphere (excitatory anodal tDCS; A-tDCS) and/or suppressing activity in the undamaged hemisphere (cathodal tDCS; C-tDCS) [11-13] for facilitating the recruitment of perilesional regions to subservise language processing. Maximum gains with such a passive neuromodulation may be obtained after combining it with impairment-oriented behavioural therapy [4,7,10].

At the present state of research, it is still unclear whether neural mechanisms supporting language abilities following brain injury can be effectively modulated using different modes, parameters and number of sessions of tDCS depending on such important factors determining recovery from aphasia as lesion site and size, duration of illness, as well as type and level of impairment [4,10,14]. In choosing the stimulated area or adjusting current dosage and parameters for optimal clinical effect, modern neurophysiological and neuroimaging methods of indexing cortical excitability may be potentially useful. However, their utility and/or possibility of integrating with tDCS devices (which also have their own drawbacks such as widespread stimulation effect, reduced depth of penetration, and low control of target location) are still

limited [15]. Given these difficulties, so far a small but growing body of evidence suggests that tDCS may be beneficial in chronic stroke patients with aphasia, but the data are inconclusive [16-22]. Very little is known about the impact of tDCS on aphasia recovery in the early stages of stroke, when activity imbalance of both hemispheres is usually the highest and the most susceptible to change [23]. In the only study of this type [24] inhibitory stimulation of the right temporal cortex seemed to be effective, but activation of the mirror structures of the left hemisphere was functionally insignificant.

In our study, we aimed to explore whether repeated excitatory A-tDCS applied over the left posterior inferior frontal cortex (Broca region, indicated as essential for language in nearly all aphasics and a critical area in aphasia neuromodulation protocols) [25,26] could ameliorate the symptoms of aphasia in post-stroke patients in the early stage of neurorehabilitation (less than six months), when most recovery is observed at neurophysiological and functional levels [1,23]. We explored this issue in a single-centre, randomized, double-blind, sham-controlled trial.

## Material and methods

### Study participants

Participants were recruited from patients consecutively admitted to the Neurorehabilitation Unit within a three-year period (from May 2009 to May 2012). Those who met the inclusion criteria and agreed to participate in the study were randomly assigned to either the experimental group receiving language therapy in combination with excitatory A-tDCS, or the control group receiving the therapy with sham stimulation. Inclusion criteria were as follows: (1) male and female patients under 75 years of age; (2) first-ever middle cerebral artery ischaemic stroke in the language-dominant left hemisphere (confirmed by magnetic resonance imaging [MRI] or computed tomography); (3) time from onset of symptoms 2-24 weeks; (4) premorbidly right-handed; (5) moderate to severe aphasia symptoms (confirmed in a neuropsychological assessment). Exclusion criteria were: (1) unstable somatic conditions; (2) concomitant neurological or psychiatric illnesses; (3) epileptiform EEG activity; (4) current use of medication that could affect cortical excitability (e.g., antipsychotics or antidepressants); (5) contraindications to electrostimulation (e.g. metal implants in the head, no tolerance to currents, acute eczema under the electrodes).

Among 40 included participants, 37 completed the rehabilitation programme (92.5%; two were excluded because of a recurrent stroke, one resigned because of personal problems), and 33 took part in a follow-up study (82.5%; difficulty in re-establishing contact with four patients after their discharge from hospital). Participants' demographic and clinical characteristics are summarized in Table 1.

Ethical approval for the research programme was obtained from the local Bioethics Committee. All patients provided their written informed consent to participate in the study.

### Procedure

Patients from both groups underwent the same evaluation of the type and level of aphasia and its functional consequences, as well as received the same type of language therapy and number of rehabilitation sessions. Assessment of aphasic symptoms was performed three times: before the rehabilitation (pre-treatment assessment), after its completion (post-treatment assessment) and three months later (follow-up assessment) using the Polish version of a short form of the Boston Diagnostic Aphasia Examination (BDAE) [27,28]. Based on pre-treatment assessment, containing in addition to the BDAE, the 6-grade Aphasia Severity Rating Scale (ASRS) [27,28], patients were classified as having moderate to severe fluent or non-fluent aphasia with functional communication problems ranging from '1' (all communication is through fragmentary expression) to '4' (some obvious loss of fluency in speech or facility of comprehension).

The rehabilitation programme consisted of fifteen consecutive (five times a week for three weeks) 45-min language therapy sessions, preceded by 10-min tDCS (A-tDCS in experimental group, sham stimulation in control group). During the language therapy, progressive exercises were used from the Polish computerized system for rehabilitation of aphasic patients (Afasystem, Harpo Sp. z o.o., Poznań, Polska) under the supervision of a professional therapist. The exercises included speech initiation, verbal comprehension, word finding, word-picture matching, repetition of words or sentences, building grammatically and syntactically correct sentences, as well as reading and writing. Although the general nature of this therapy was similar for all patients, the type and difficulty of specific exercises varied depending on the character and severity of aphasic symptoms. Thirty-one patients suffering from motor

**Table 1.** Baseline demographic and clinical characteristics of both groups\*

Variable	Experimental group (n = 18)	Control group (n = 19)	P value
Age [years]	57.6 ± 9.6 (59, 34-75)	62 ± 11.9 (66, 35-75)	0.22 <sup>a</sup>
Education [years]	14.9 ± 3.6 (15, 11-22)	13.8 ± 3.4 (13, 8-20)	0.6 <sup>b</sup>
Time since stroke [days]	55.7 ± 44.8 (46, 10-187)	63.5 ± 43.1 (54, 10-175)	0.4 <sup>b</sup>
Barthel index	12.5 ± 7.8 (14.5, 1-20)	15.2 ± 7.1 (20, 2-20)	0.19 <sup>b</sup>
ASRS	2 ± 1.1 (2, 1-4)	2.3 ± 1 (2, 1-4)	0.41 <sup>b</sup>
Lesion volume [cm <sup>3</sup> ]	46.8 ± 33.7 (48.5, 3.4-109.8)	52.7 ± 48 (31.6, 3.6-152.9)	0.93 <sup>b</sup>
BDAE-naming (max: 72)	37.9 ± 22.8 (33, 3-72)	40.4 ± 22.3 (48, 2-72)	0.74 <sup>a</sup>
BDAE-comprehension (max: 61)	45.9 ± 12.7 (47, 18-61)	46.3 ± 11.7 (46, 21.5-60)	0.92 <sup>a</sup>
BDAE-repetition (max: 13)	8.2 ± 3.9 (8, 2-13)	8 ± 3.4 (9, 0-12)	0.8 <sup>b</sup>
Gender (male/female)	11/7	13/6	0.9 <sup>c</sup>
Aphasia (fluent/non-fluent)	4/14	9/10	
Lesion:			
Frontal	12	10	
Temporal	7	12	
Parietal	10	7	
Occipital	1	0	
Insular	2	1	
Subcortical	10	9	

\*Data are shown as mean ± standard deviation, median (interquartile range) or as absolute numbers

ASRS – Aphasia Severity Rating Scale; BDAE – Boston Diagnostic Aphasia Examination

<sup>a</sup>Student *t*-test; <sup>b</sup>Mann-Whitney *U*-test; <sup>c</sup>χ<sup>2</sup> test

deficits co-occurring with aphasia additionally received 45-min physiotherapy each day; the others (six patients) participated in occupational therapy as an equivalent.

After the rehabilitation programme (between post-treatment and follow-up assessments), we controlled the amount of aphasia therapy only if it was provided in formal settings. However, all patients were encouraged to continue training at home after discharge. The number of hours of these individual home exercises was not monitored.

An independent researcher was responsible for the random assignment of subjects to the experimental or control group and for tDCS delivery. For allocation of participants, a procedure of stratified randomization with minimization was used to ensure balance between groups in terms of age, severity of language impairment, and time since stroke. Two members of the research team (KP, neuropsychologist and language therapist, who conducted aphasia assessments and led language therapy; and ML, neuropsychologist and data analyst) and study participants were blinded to the allocation. To ensure

blinding of the type of treatment for patients, arrangement of electrodes and the time they remained on the head were the same in both groups, the DC stimulator was covered after it had been switched on and 10 minutes later it was switched off, and all participants were temporarily subjected to direct current to provide similar sensations associated with light irritation of skin sensory receptors [29].

### Transcranial direct current stimulation (tDCS)

The tDCS protocol followed the work of Nitsche and co-workers concerning arrangement of electrodes, safety tDCS in human studies [30], and tDCS duration-dependent shifts in cortical excitability during and after stimulation [31].

The current was delivered by a battery-driven stimulator (NeuroConn, 1 channel DC Stimulator Plus, Germany) at 1-mA intensity using a pair of surface saline-soaked 35-cm<sup>2</sup> (5 × 7 cm) sponge electrodes. The excitatory anodal electrode was placed over the pos-

terior inferior frontal cortex of the left hemisphere (Broca language region defined as the crossing point between T3-Fz and F7-Cz according to the 10-20 EEG system for electrode placement), and the reference (cathodal) electrode was placed above the right supraorbital area, providing a current flow through the brain and other tissues of the head from the anode to the cathode. This localization method has been used before in tDCS studies [21,26].

The experimental group received fifteen sessions of real A-tDCS (1 mA for 10 min; current density = 0.028 mA/cm<sup>2</sup>), while the control group received the same number of sham A-tDCS (1 mA for first 25 s of 10-min stimulation period). Real stimulation was expected to induce cortical excitability elevations both during stimulation (an effect of the shifts in resting membrane potentials in underlying neurons) and after its completion (an effect of potentiation of N-methyl-D-aspartate action). The latter was anticipated to remain for up to one hour after the stimulation, and to be prolonged and stabilized due to repetition of stimulation [11-13,31]. Since tDCS typically makes use of large electrodes, it is likely that both the lesion and the surrounding frontotemporal regions were stimulated [10,16,21] with probable spreading of the activation from Broca region throughout the rest of the language network [32].

The procedure of different exposure to the current action ensured that all participants could feel a slight itching sensation on the scalp that usually faded over seconds after starting the device [29,31], but prevented efficient modulation of cortical excitability in the control group. Additionally, current intensity was gradually increased (at the beginning of the session) and decreased (at the end of the session) to diminish its perception.

### Outcome measurement

For assessment of aphasic symptoms, the short version of the BDAE in the Polish adaptation [28] was used. This is one of the most popular batteries for clinical use and is divided into four sections (each containing several subtests): auditory comprehension, oral expression, understanding written language, and writing. BDAE outcome measures consisted of total scores from subtests evaluating the most important language skills: naming (subtests: Responsive Naming, Visual Confrontation Naming), comprehension (subtests: Verbal Discrimination, Body-Part Identification, Commands, Complex Ideational Material), and verbal rep-

etition (Repetition of Words, Repetition of Phrases and Sentences). The numerical results of naming and comprehension subtests include the degree of accuracy and speed of verbal responses; results of repetition subtests depend only on the accuracy of reactions.

### Statistical analysis

Data analyses were performed with the SPSS software package (v.15). Differences in categorical data were analysed using the  $\chi^2$  test. Depending on the type of distribution (assessed by the Shapiro-Wilk test and exploration of histograms and normal Q-Q plots), either Student *t*-test or the Mann-Whitney *U* statistic were used to compare the average values of baseline characteristics of the experimental and control groups. The short-term and long-term efficacy of the applied therapy was assessed using a mixed (between-within) model ANOVA (with *time of assessment* as a within-group factor and *intervention* as a between-group factor). If the normality of variable distribution was not confirmed in either of the groups, their average scores were compared using the Mann-Whitney *U*-test, and the scores from consecutive assessments were compared using the Wilcoxon signed-rank test. All tests were two-sided and *P* value < 0.05 was considered statistically significant. However, to control for multiple comparisons when analysing long-term changes (follow-up), the Bonferroni correction was applied. Therefore, when two comparisons were made,  $\alpha$  was set at 0.025, and in the case of three comparisons it was set at 0.017. Additionally, effect sizes were determined using Cohen's *d* (mean change score divided by pooled standard deviation) or partial  $\eta^2$  according to Cohen's criteria [33]. As proposed by Cohen [34], effect sizes of 0.2 to 0.5 were considered small, 0.5 to 0.8 were moderate, while those greater than 0.8 were large.

### Results

Both groups were balanced at baseline with respect to age, years of education, severity of aphasic symptoms (BDAE: naming, comprehension, repetition; ASRS), time since onset, lesion volume, and functional status as measured by the Barthel index (BI) [35]. The proportion of men and women as well as various lesion locations were balanced, while there were more non-fluent than fluent aphasics in the experimental group (Table 1). There were no significant intergroup differences in outcome measure scores at baseline (Table 2).

**Table 2.** Results of the Boston Diagnostic Aphasia Examination in each assessment

	Pre-treatment assessment	Post-treatment assessment	3-month follow-up assessment				
	Mean $\pm$ SD	Mean $\pm$ SD	$d_1$	$P_1$	Mean $\pm$ SD	$d_2$	$P_2$
<b>BDAE-Naming</b>							
Experimental group ( $n = 18$ )	37.9 $\pm$ 22.8	49.7 $\pm$ 18.8	0.56	0.001 <sup>a</sup>	50.7 $\pm$ 23.6	0.5	0.01 <sup>c</sup>
Control group ( $n = 19$ )	40.4 $\pm$ 22.3	47.7 $\pm$ 21.8	0.33	0.001 <sup>a</sup>	47.3 $\pm$ 22.6	0.31	0.004 <sup>c</sup>
$P$ between groups	0.74 <sup>b</sup>	0.26 <sup>a</sup>			0.72 <sup>c</sup>		
<b>BDAE-Comprehension</b>							
Experimental group ( $n = 18$ )	45.9 $\pm$ 12.7	50.7 $\pm$ 11.5	0.4	0.001 <sup>c</sup>	51.2 $\pm$ 11.6	0.44	0.001 <sup>a</sup>
Control group ( $n = 19$ )	46.3 $\pm$ 11.7	50.1 $\pm$ 13	0.31	0.019 <sup>c</sup>	52.9 $\pm$ 8.6	0.64	0.001 <sup>a</sup>
$P$ between groups	0.92 <sup>b</sup>	0.94 <sup>c</sup>			0.38 <sup>a</sup>		
<b>BDAE-Repetition</b>							
Experimental group ( $n = 18$ )	8.2 $\pm$ 3.9	10.3 $\pm$ 2.9	0.61	0.005 <sup>c</sup>	10.1 $\pm$ 3.8	0.49	0.006 <sup>c</sup>
Control group ( $n = 19$ )	8 $\pm$ 3.4	8.5 $\pm$ 3.7	0.14	0.32 <sup>c</sup>	9.2 $\pm$ 4.3	0.31	0.015 <sup>c</sup>
$P$ between groups	0.8 <sup>c</sup>	0.09 <sup>c</sup>			0.25 <sup>c</sup>		

SD – standard deviation; BDAE – Boston Diagnostic Aphasia Examination

$d_1$  – Cohen's  $d$  calculated for pre-treatment and post-treatment scores;  $d_2$  – Cohen's  $d$  calculated for pre-treatment and follow-up scores

$P_1$  – significance of difference between pre-treatment and post-treatment scores;  $P_2$  – significance of difference between pre-treatment and follow-up scores

<sup>a</sup>mixed (between-within) model ANOVA; <sup>b</sup>Student  $t$ -test; <sup>c</sup>Mann-Whitney  $U$ -test; <sup>d</sup>Wilcoxon signed rank test

After a three-week rehabilitation programme, both groups significantly improved in almost all language outcome measures (Table 2). However, there were no statistically significant differences between the experimental and control groups either in naming function ( $F(1, 35) = 1.33$ ,  $P = 0.26$ , partial  $\eta^2 = 0.04$ ) or comprehension ( $U = 168.5$ ,  $P = 0.94$ ) or repetition ( $U = 114.5$ ,  $P = 0.09$ ). The control group obtained small effect sizes in all outcome measures, while effect sizes for the experimental group in BDAE-Naming and BDAE-Repetition were moderate. Overall, effect sizes in the experimental group were higher in all three outcome measures.

The analysis of test scores in follow-up assessment revealed no statistically significant differences between the groups, although the scores were still significantly better as compared to the baseline evaluation. The groups did not differ in naming ( $U = 104$ ,  $P = 0.72$ ), comprehension ( $F(1, 28) = 0.787$ ,  $P = 0.38$ , partial  $\eta^2 = 0.027$ ) or repetition ( $U = 85.5$ ,  $P = 0.25$ ). The experimental group obtained higher effect sizes in two outcome measures (naming and repetition). The effect size in the control group proved higher in comprehension.

In order to test the initial hypothesis on a relatively homogeneous group, we selected patients with predominant anomic symptoms. This subgroup included 10 patients with Broca's aphasia and 3 patients with

anomic aphasia. There were 6 such participants in the control group and 7 in the experimental group. We compared their BDAE-Naming scores and found no statistically significant differences either before treatment ( $U = 18$ ;  $P = 0.67$ ), after treatment ( $U = 17$ ;  $P = 0.57$ ) or at 3-month follow-up ( $U = 8.5$ ;  $P = 0.23$ ).

## Discussion

Results of the present randomized, double-blind, sham-controlled pilot study did not confirm the preliminary hypothesis that multiple applications of excitatory A-tDCS over Broca area, if combined with language therapy, can improve the dynamics of recovery in the early period of post-stroke aphasia rehabilitation. Although both real and sham-stimulated groups significantly improved their language performance after the rehabilitation period, we found no significant differences between groups in either short- or long-term effects of A-tDCS in either of the outcome measures. This finding is contrary to previous studies showing that A-tDCS applied over the frontal [16,19] or temporal cortex of the stroke-affected left hemisphere improved naming ability in chronic fluent and non-fluent aphasic patients. However, our results are in accordance with

a study conducted in subacute stroke patients with global aphasia, in which anodal activation of the temporal cortex of the lesioned left hemisphere proved ineffective in contrast to cathodal suppression of the intact right hemisphere [24]. Although the above-mentioned studies differ from our study in many aspects, our results seem to be interesting in their context, and suggest new directions for further research.

The lack of significant differences in language outcomes between groups, which was found in our study, might reflect insufficient A-tDCS intensity too limited to elicit significant behavioural gains of current-induced neuromodulation, or the problem might lie in detecting the influence of weak stimulation on patients' dynamic recovery in the early stage of spontaneous recovery, which may cover the A-tDCS effect. Many findings, coming especially from studies on motor cortex stimulation, show that behavioural effects of tDCS do not directly mirror robust electrophysiological effects [36], which are associated in turn with current polarity and density, duration and frequency of stimulation sessions, and electrode positions [15,31]. The hypothesis of insufficient neuromodulation in our study may be supported by a relatively short administration of 1 mA tDCS (10-min in contrast to 20-min stimulation in previous experiments), and lack of precise identification of the most language-eloquent perilesional cortex (e.g. with functional MRI [fMRI]) to be stimulated by the anode, which characterized successful studies of Baker [16], and Fridriksson [19] that describe positive effects of A-tDCS in chronic aphasics. However, the number of A-tDCS sessions important for the cumulative effect was greater than in other studies. Similarly, 10 sessions of even more intensive stimulation (2 mA, 30 min), used by You and co-workers [24], did not lead to significant functional changes in individuals at the early stage of recovery after stroke. This might suggest the importance of the phase of stroke recovery in which the stimulation is introduced.

The inefficiency of tDCS in our study may also result from the specificity of the stimulation mode. The lack of influence of the anodal stimulation on language abilities detected in our study is accompanied in other studies by positive effects of the cathodal tDCS applied to the same lesional area [21] or the contralesional intact cortex [24]. Indeed, a growing number of human studies [37] and animal experiments [38] confirm that in the central nervous system it is easier to induce excitability-diminishing neuroplastic alterations than to enhance excitability [11]. Furthermore, neurophysiological and

anatomical changes in the affected hemisphere following stroke could disrupt the electric current by tDCS and therefore anodal stimulation of the damaged hemisphere might lead to unpredictable effects both on brain activity and at a functional level [22,34]. Anomalies in distribution of currents may potentially explain the surprising results in Monti's study [21] in which cathodal, but not anodal stimulation of Broca area produced improvements in non-fluent aphasic patients. It should also be considered whether too early modulation of cortex excitability may be harmful in some conditions. Animal studies show that hyperexcitability of the surrounding tissue in the very early post-stroke period makes surrounding neurons vulnerable to excitation. In the presence of excitatory and toxic substances from the ischaemic tissue, additional release of excitatory factors may lead to tissue loss, although not significantly affecting the functional outcome [39].

Speculating on the possible causes of the insufficient A-tDCS impact on language abilities in our study, one should also take into account the nature of neurological recovery in the early stages of stroke. Dynamic spontaneous recovery [40] from aphasia observed during the first six months after stroke is responsible for most functional improvements [1,2,41]. The scale of functional changes may jeopardize the detection of effects of the applied rehabilitation interventions, in particular when they are relatively small as compared to the heterogeneous amount of spontaneous recovery. Transcranial application of weak direct currents, polarizing underlying tissue in physiological limits, may appear insufficient to notice a clear difference at the behavioural level. Although we controlled non-specific effects by using a sham tDCS and measured various language parameters (accuracy, reaction time), patients from both experimental and control groups significantly improved in assessed skills within three weeks when therapy was conducted, but we found no significant differences between groups that could indicate an advantage of the type of tDCS tested in our study. It should be noted, however, that the slightly greater effect sizes in the experimental group may reflect some minimal response to the neuromodulatory intervention. This justifies further attempts to investigate potential benefits of A-tDCS for language recovery after stroke.

The present study has several limitations: (1) small sample size, although it remains the largest among similar studies conducted to date (37 versus 3 to 21 participants in the other studies); (2) application of the anode electrode over Broca's area according to the 10-20 EEG

system, while new findings suggest that such stimulation may be more beneficial when the anode is applied over preserved cortex with the highest level of activation during a language task (e.g. determined during a pretreatment fMRI simple language task – a procedure difficult for general use in neurorehabilitation centres so far); and (3) potentially unwanted excitability changes in the tissue underlying the reference electrode mounted on the forehead, which may affect recovery from aphasia.

Our findings, as well as those from previous studies, raise several questions important for future research:

- What safe parameters of enhancing neuromodulation of the damaged hemisphere would produce considerable functional gains early after stroke when spontaneous autoregulation of disrupted neuronal networks masks the influence of other factors?
- Is enhancement or rather an alternative inhibition strategy better for reactivation of spared networks of the left-hemisphere language system?
- Would the effects of enhancing stimulation have been more pronounced if the exact location (based e.g. on fMRI) of the language-eloquent areas had been chosen as coordinates for stimulation?

These questions, fundamental from the neurorehabilitation perspective, should be addressed in future single- and multicentre trials before direct current treatment can be considered a standard neurophysiological supplement of behavioural aphasia therapy.

## Conclusions

The findings do not support A-tDCS functional benefits during early rehabilitation of post-stroke aphasia. Further research is needed to explore the effectiveness of this kind of neuromodulation.

## Disclosure

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