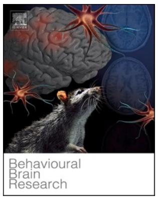
Behavioural Brain Research 399 (2021) 113019

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr



Spinal or cortical direct current stimulation: Which is the best? Evidence from apraxia of speech in post-stroke aphasia

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ARTICLE INFO

Keywords:
Transpinal stimulation
Apraxia of speech
Language recovery
Neuromodulation

ABSTRACT

To date, new advances in technology have already shown the effectiveness of non-invasive brain stimulation and, in particular, of transcranial direct current stimulation (tDCS), in enhancing language recovery in post-stroke aphasia. More recently, it has been suggested that the stimulation over the spinal cord improves the production of words associated to sensorimotor schemata, such as action verbs. Here, for the first time, we present evidence that transpinal direct current stimulation (tsDCS) combined with a language training is efficacious for the recovery from speech apraxia, a motor speech disorder which might co-occur with aphasia. In a randomized-double blind experiment, ten aphasics underwent five days of tsDCS with concomitant treatment for their articulatory deficits in two different conditions: anodal and sham. In all patients, language measures were collected before (T0), at the end (T5) and one week after the end of treatment (F/U). Results showed that only after anodal tsDCS patients exhibited a better accuracy in repeating the treated items. Moreover, these effects persisted at F/U and generalized to other oral language tasks (i.e. picture description, noun and verb naming, word repetition and reading). A further analysis, which compared the tsDCS results with those collected in a matched group of patients who underwent the same language treatment but combined with tDCS, revealed no differences between the two groups.

Given the persistency and severity of articulatory deficits in aphasia and the ease of use of tsDCS, we believe that spinal stimulation might result a new innovative approach for language rehabilitation.

1. Introduction

Speech is one of the most complex and fully exercised motor skills in humans. All normally developing individuals learn it from birth on and exercise speech motor behaviour day by day, over their whole lifetime [1–3]. According to Levelt's theory [1], in any language, the frequent use of the same articulatory gestures participating in the construction of words transforms the correspondent motor pattern into a stable, overlearned movement program represented onto the motor-cortical hard-disk which stores the human's phonetic lexicon [1,4].

Focal brain damage to the dominant (typically left) hemisphere can cause an alteration in this orchestration of movements, knows as "apraxia of speech" (AOS) [5–9]. AOS is an acquired motor speech disorder characterized by an impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sounds [10–12]. Darley first described AOS as "a disorder of motor speech programming manifested primarily by errors in articulation" [13]. It varies from a complete inability to articulate any given syllable and/or word to distortions of consonants and vowels that may be perceived as sound substitutions in the absence of reduced strength or tone of muscles and articulators controlling phonation [14,15]. Over the last decades, a variety of treatment approaches has been developed to remediate the AOS disorder with no one approach proved to be effective for all patients [16–18]. For patients with moderate to severe AOS, therapy is mostly focused on relearning oral postures of individual speech sounds through nonwords (i.e. syllables) and words repetition. Indeed, repetition is a multistage process dependent upon the left-dominant dorsal pathway which maps sound-based codes to articulatory codes which involves pre-articulatory planning in Broca's area and subsequent planning of articulatory gestures prior to motor execution in the premotor and motor cortices [19,20]. Thus, nonword and word repetition results specially adapted to the needs of patients with AOS disorders [21–26]. Accordingly, studies in patients with AOS have suggested that together with a damage to the Broca's area [7,27,28], impairment to other brain

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https://doi.org/10.1016/j.bbr.2020.113019
Received 22 December 2019; Received in revised form 4 September 2020; Accepted 11 November 2020

structures, such as the left anterior insula [6,28] and the premotor and motor regions [29–34] leads to AOS. A recent voxel-based lesion mapping study by Basilakos and colleagues [33] revealed that the pattern of brain damage associated with AOS is most strongly associated with damage to the left cortical motor regions, with additional involvement of the left somatosensory areas [35,36]. Thus, taken together, all of these results point to a crucial role of the sensorimotor network in speech articulation [37].

In more recent years, new advances in technology have shown that transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique, results efficacious in the recovery of different cognitive abilities [38–40] among which language in aphasic individuals [41,42]. During tDCS weak polarizing direct currents are delivered to the cortex via two electrodes placed on the scalp. The nature of the effects depends on the polarity of the current. Generally, the anode increases cortical excitability when applied over the region of interest with the cathode above the contralateral orbit or above the shoulder (as the reference electrode), whereas the cathode decreases it, limiting the resting membrane potential. These effects may last for minutes to hours depending on the polarity, duration and intensity of stimulation and they are generally compared with a placebo condition (the so-called “sham” condition) in which the stimulator is turned-off after 30 s [43]. With regard to AOS disorder, previous tDCS studies have shown that bihemispheric tDCS, with simultaneous excitatory stimulation over the left inferior frontal gyrus and inhibition over the right homologous, combined with a repetition language training improves the patients’ performance not only in terms of better accuracy in articulating the treated stimuli but also for untreated items on different language tasks (picture description, noun and verb naming, word repetition, word reading) [8,9]. Moreover, according with the hypothesis of a sensorimotor involvement [4,30–34,37], in the Marangolo et al. study [9], anodal stimulation exerted stronger functional connectivity changes into the left premotor and motor areas and in the left cerebellum compared to sham [9].

Given that speech articulation requires the involvement of motor planning [1,33,34], in the present study, we wondered whether other auxiliary systems functionally connected to the brain, which process sensorimotor information, might facilitate the recovery of AOS. Indeed, it has already been shown that spinal cord stimulation induces neurophysiological modifications at the cortical level through the activation of tonic afferent pathways to the cortex [44–46]. In particular, transpinal direct current stimulation (tsDCS) applied over the thoracic vertebrae (T9-T11 level, 2 mA, 20 min) induced supraspinal effects by modulating intracortical excitability in the motor cortex. Anodal tsDCS decreased motor-evoked potentials (MEPs), while cathodal tsDCS elicited opposite effects [44,47,48]. Accordingly, recent modeling studies have proved that, despite some inter-individual differences, the electric field induced by thoracic tsDCS is longitudinally directed along the vertebral column, especially when the return electrode is placed over the right arm [49,50]. Yet, the electric field induced by thoracic tsDCS is maximum at thoracic level and it increases somatosensory activity from the spinal cord to the brain [49,50]. More recently, by using resting state functional imaging (rs-fMRI), Schweizer and co-workers [51] investigated whether tsDCS-induced reported changes in neurophysiological measures [44,45,47,48] might also be reflected in spontaneous brain activity. In their study, resting state functional connectivity was measured in twenty healthy subjects by using blood oxygenation level-dependent, functional magnetic resonance imaging before and after anodal, cathodal, and sham tsDCS (20 min, 2.5 mA) with the active electrode centered over the thoracic vertebrae (T9-T11). As compared with sham, anodal tsDCS resulted in connectivity changes into the somatosensory cortex (S1) and the ipsilateral posterior insula for both left and right hemispheres. Additional changes were present in the thalamus and in the anterior cingulate cortex. Thus, these results provide further evidence for supraspinal effects induced by tsDCS suggesting that spinal stimulation might be considered as a new noninvasive intervention for targeting cortical networks [51].

To the purpose of our study, given that speech articulation requires the activation of motor plans [1–3] and that tsDCS induces changes into cortical areas [44,45,47,51] involved in speech articulation [6,28,33], we might hypothesize that spinal stimulation, by influencing activity into the sensorimotor networks, would result efficacious for AOS recovery.

In line with this hypothesis, very recently, in a group of fourteen chronic aphasics, Marangolo et al. [46] have shown that anodal tsDCS delivered over the thoracic vertebrae combined with a picture naming task led to a greater increase of words related to sensorimotor schemata, such as action verbs (i.e. *to run*), compared to nouns not typically related to specific action (i.e., *the cloud*). More importantly, in a more recent rs-fMRI study [52], the authors found that the amount of verb improvement found after anodal tsDCS significantly correlated with supraspinal functional changes into a cerebello-cortical network which specifically influenced regions, such as the left premotor cortex and the left cerebellum known to be involved in motor processing [53,54].

Thus, given all of the above evidence, in the present study we wanted to investigate if tsDCS combined with a repetition training would facilitate AOS in post-stroke aphasic individuals.

2. Materials and methods

2.1. Participants

Ten patients with chronic aphasia (6 females and 4 males) who had suffered a single left hemisphere stroke were included in the study. All participants were native Italian speakers with right premorbid manual dominance (based on the "Edinburgh Handedness Questionnaire" [55]), they were all affected by a single left hemispheric stroke occurred at least 6 months prior to experimentation. Subjects over 75 years of age with seizures, previous brain injuries, possible spinal cord comorbidity and any type of implanted electronic device (e.g. pacemaker) were excluded. None of the participants has received structured language therapy for at least 6 months before the time of inclusion in the study in order to prevent confounding therapy effects.

2.2. Ethics statement

The data analysed in the current study were conformed with the Helsinki Declaration. Our named Institutional Review Board (IRCCS Fondazione Santa Lucia, Rome-Italy) specifically approved this study with the understanding and written consent of each subject.

2.3. Clinical data

In all patients, magnetic resonance imaging showed an ischemic lesion involving the left hemisphere. All patients presented non-fluent speech with severe AOS. Subjects were not able to produce any words in spontaneous speech. Their language production was limited to a few syllables with severe articulatory groping and distortions of phonemes in naming, repetition and reading tasks of twenty simple syllables (e.g. PA, MA, FU) and words [e.g. pipa [pipe]), casa [home] of a standardised test for the evaluation of articulation [56]. To thoroughly investigate the aphasics’ language performance, each participant was also administered a standardized language test (Esame del Linguaggio II [57]). Articulatory errors and distortions of phonemes were present in naming, repetition and reading aloud. Noun and verb written naming and word writing under dictation were also severely impaired. Auditory comprehension abilities were adequate for simple words and commands in the language test (Esame del Linguaggio II [57]), while patients experienced significant difficulties in more complex auditory comprehension tasks (Token test cut-off 29/36 [58];). To evaluate nonverbal oral motor skills, the Buccofacial Apraxia Test was also administered [59]. None of the patients showed buccofacial apraxia (see Table 1).

Table 1
For each language task, the percentage of correct responses are reported (Esame del Linguaggio II, cut-off 100 %, Ciurli et al., 1996).

P	Sex	Age	Ed. Level	Time post onset	PD	NN	VN	WR	NWR	W Read	NW Read	WNN	WVN	WD	NWD	TT
1	F	65	8	7y 2mo	0	5	5	2,5	0	2,5	10	15	5	2,5	0	12
2	F	75	8	2y	0	5	5	5	5	5	0	0	0	5	0	14
3	F	73	18	12y	0	0	0	5	5	0	0	0	0	0	0	10
4	F	64	13	6y 6mo	0	2,5	0	2,5	0	5	15	0	0	5	5	12
5	F	68	18	1y 2mo	0	0	2,5	0	0	5	5	0	0	0	0	18
6	M	56	13	2y 6mo	0	0	0	0	0	0	0	0	0	0	0	14
7	F	70	5	4y	0	7,5	10	10	7,5	0	0	0	0	5	0	15
8	M	51	13	8mo	0	0	0	5	5	5	5	5	0	5	5	12
9	M	58	8	8mo	0	0	0	0	0	10	15	0	0	5	0	14
10	M	61	13	1 y 7mo	0	0	0	0	0	0	0	0	0	0	0	14

Legend: Ed.Lev. = Educational Level; G = Gender; PD = Picture Description; NN = Noun Naming; VN = Verb Naming; WR = Word Repetition; NWR = Non word Repetition; W Read = Word Reading; NW Read = Non word Reading; WNN = Written Noun Naming; WVN = Written Verb Naming; WD = Word under Dictation; NWD = Non Word under Dictation; TT = Token Test (cut-off score 29/36).

2.4. Materials

Two lists of 90 stimuli each were prepared. Each list included 28 CV syllables (eg. MA, NA, RI), 15 CCV syllables (eg. STA, TRA, PLE), 25 CVCV and CVCCV bysillabic words (eg. pipa (pipe), luna (moon), nonno (grandfather), panna (cream)), 12 CVCVCV trisyllabic words (eg. tavolo (table), limone (lemon)) and 10 sentences made of the syllables and words presented in the list (eg. il nonno fuma la pipa (the grandfather smokes the pipe)). According to the International Phonetic Alphabet [60], syllables included different places (eg. plosive, nasal, fricative) and manners of articulation (eg. bilabial, dental, velar).

2.5. Procedure

2.5.1. Transcutaneous spinal direct current stimulation

tsDCS was applied using a battery driven Eldith (NeuroConn GmbH, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the 10th thoracic vertebra (spanned from the ninth to the 11th thoracic vertebrae) while the reference electrode was positioned over the right shoulder on the deltoid muscle. For sham stimulation, the same electrodes position was used. The current was ramped up to 2 mA and slowly decreased over 30 s to ensure the typical initial tingling sensation [61]. Since in previous works it was shown that only anodal tsDCS exerted a significant improvement on verb recovery [46,52], only two experimental conditions were used: anodal tsDCS and sham. All patients underwent the two conditions in a randomized double-blind procedure. Both the experimenter and the patient were blinded with respect to the stimulation condition and the stimulator was turned on/off by another person. At the end of each condition, none of the participants was able to notice differences in the intensity of sensation between the two conditions, not being aware of what condition they were performing [62]. In both conditions, patients underwent concurrent speech therapy for their articulatory disorders. The language treatment was performed in five daily sessions (Monday to Friday). There was 14-day intersession interval between the real and the sham condition. The assignment of each list of stimuli (N = 90) to each stimulation condition (anodal vs. sham) was randomized across conditions and the order of stimuli presentation was randomized between treatment sessions.

2.5.2. Language treatment

For each condition, patients were administered all the standardized language tests at the beginning (baseline; T0), at the end (T5) and 1 week after the end of treatment (follow-up; F/U). Once the electrodes were placed, subjects performed the language treatment for their articulatory disorders. Different from our previous published studies [46,52], whose aim was to enhance verb production, here, we wanted to restore the patient's ability to translate speech plans into its correspondent motor programs in order to improve speech articulation. Thus, we chose a very simple repetition task which requires to translate the incoming sensory information (i.e. the auditory target) into its outgoing motor production [14–18].

The therapy method was similar for all patients (for the same method see also [8,63]). For each condition, the entire list of stimuli was presented in each daily session. The therapist and the patient were seated face to face so that the patient could watch the articulatory movement of the therapist as she spoke. The therapist presented one stimulus at a time and the treatment involved four consecutive steps, which were designed to progressively induce the patient to reproduce correctly the stimulus. Step 1: The clinician auditorily presented the whole stimulus and asked the patient to repeat it. If the patient correctly repeated the stimulus, the clinician would present another stimulus, if she/he made errors the clinician would move on the next step. Step 2: The clinician auditorily presented the stimulus with a pause between each syllable, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same. Step 3: As in Step 2, the clinician auditorily presented the stimulus again with a pause between each syllable, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same. Step 4: The clinician auditorily presented one syllable at a time, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same. Step 5: As in step 4, the clinician auditorily presented one syllable at a time again, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same. Each participant's response was transcribed and recorded on audiotape. In order to assure the double-blind procedure, all responses, without any identification label, were analysed by an independent external examiner, who was totally unaware of the aim of the treatment and/or of the experimental condition (anodal vs. sham) to which the patient has been subjected. Responses were scored as correct only if all sounds in the syllables, words or sentences were correctly articulated.

2.6. Data analysis

The patients' performance was evaluated by taking into account the mean percentage of response accuracy for syllables, words and sentences. Data were analysed using SPSS 17.0 software. Three repeated measures ANOVAs were performed separately for syllables, words and sentences. For each analysis, two "within" factors were considered: TIME (baseline (T0) vs. end of treatment (T5) vs. follow up (FU) and CONDITION (anodal vs. sham). The post-hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of $p = < 0.05$ were considered statistically significant.

Inter-rater and intra-rater reliability were established using a two-way mixed, consistency single-measures by the intraclass correlation coefficient (ICC). For the intra-rater reliability, ICC was > 0.90 for syllables, words and sentences treatments, indicating excellent reliability.

Inter-rater reliability (IRR) was established by the primary rater and another examiner who rated patients by independently listening to speech recordings. ICC was computed for ratings on syllables, words and sentences treatments. The ICC was > 0.80 for the three treatments, indicating good reliability between the two raters.

Before and after each treatment condition, the patients' responses to the different re-administration of the standardized language tests (Esame del Linguaggio II [57]) were also analysed using χ^2-test.

3. Results

3.1. *Accuracy data*

3.1.1. *Syllables*

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,18) = 11,31, P = .001] and CONDITION (anodal vs. Sham, F (1,9) = 25,14, P = .001). The interaction TIME x CONDITION was also significant (F (2,18) = 6,86, P = .01). The Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal 33 % vs. sham 33 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal 56 % vs. sham 37 %, P = .01) and persisted at F/U (anodal 51 % vs. sham 30 % P = .00). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (4%, P = 1) (see Fig. 1).

3.1.2. *Words*

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,18) = 13,17, P = .000) and CONDITION (anodal vs. sham; F (1,9) = 23,69, P = .001). The interaction TIME x CONDITION was also significant (F (2,18) = 8,79, P = .002). The Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal: 35 % vs. sham 38 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition, at T5 (anodal 65 % vs. sham 41 %, P = .002) and persisted at F/U (anodal 54 % vs. sham 30 %, P = .003). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (3%, P = 1) (see Fig. 2).

3.1.3. *Sentences*

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,18) = 14,33, P = .000) and CONDITION (anodal vs. sham, F (1,9) = 26,57, P = .001). The interaction TIME x CONDITION was also significant F (2,18) = 5,19, P = .02). The Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal: 10 % vs. sham 10 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition, at T5 (anodal 50 % vs. sham at 20 %, P = .01) and persisted at F/U (anodal 40 % vs. sham 20 %, P = .03). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (10 %, P = 1) (see Fig. 3).

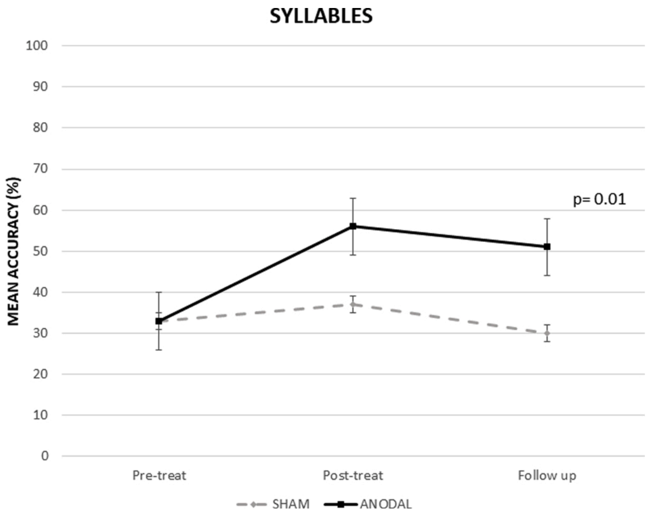

Fig. 1. Mean percentage of response accuracy for syllables at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

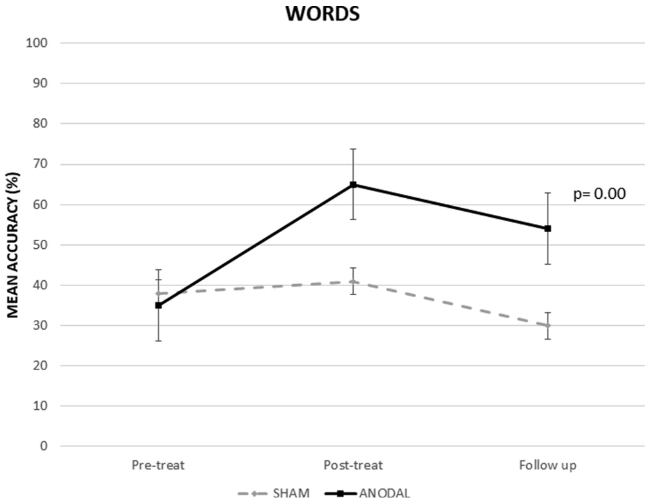

Fig. 2. Mean percentage of response accuracy for words at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

Finally, results on the "transfer of treatments effects" in the language examination indicated that, in most of the patients, there was a significant difference in the percentage of correct responses before and after the treatment in different oral language tasks, which was more pronounced after the anodal than after the sham condition (see Table 2).

3.2. *Comments*

In summary, the above results clearly suggest that tsDCS is effective for improving articulatory deficits and, more importantly, it exerts its

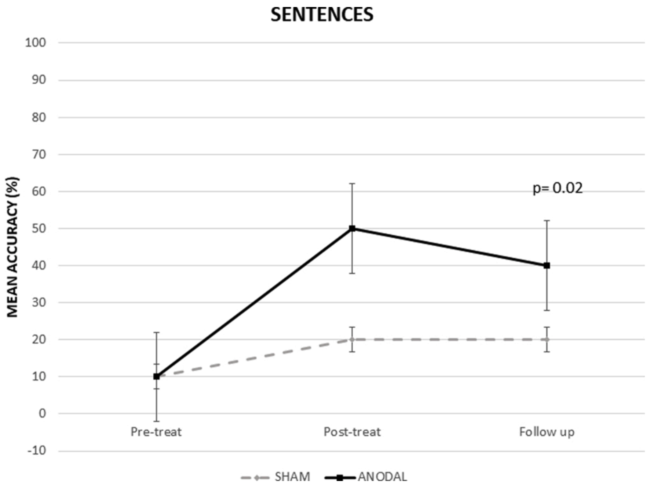

Fig. 3. Mean percentage of response accuracy for sentences at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

Table 2

Mean Percentage of Correct Responses in the Different Language Tasks (Esame del Linguaggio II, Ciurli et al., 1996) at Baseline (T0) and at the End of Treatment (T5) for the anodal and sham condition, respectively (Cut-off Score100 %).

P	C	PICTDESC	VERB N	NOUN N	W Repet	NW Repet	WRIT N	WRIT V	W READ	NWRead	W DICT	NWDICT
		T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5	T0 T5
Real First												
1	R	0 20ˆ	5 50ˆ	5 50ˆ	2,5 65ˆ	0 42,5ˆ	15 20	5 5	2,5 56,5ˆ	10 15	2,5 10	0 0
	S	20 20	50 25	50 30	65 42,5	42,5 37,5	20 25	5 7,5	56,5 42,5	15 22,5	10 15	0 0
3	R	0 0	0 10ˆ	0 25ˆ	5 52,5ˆ	5 42,5ˆ	0 2,5	0 0	0 0	0 0	0 0	0 0
	S	0 0	10 5	25 0	52,5 42,5	42,5 32,5	2,5 2,5	0 0	0 0	0 0	0 2,5	0 0
5	R	0 0	2,5 25ˆ	0 32ˆ	0 52ˆ	0 22,5ˆ	0 5	0 0	5 10	5 5	0 10	0 0
	S	0 0	25 20	32,5 40	52,5 52,5	22,5 25	5 5	0 5	50 47,5	5 0	10 20	0 0
7	R	0 0	10 20	7,5 17,5*	10 57,5ˆ	7,5 22,5**	0 0	0 0	0 10ˆ	0 5	5 10	0 5
	S	0 0	20 0	17 17	57,5 42,5	22,5 30	0 0	0 0	10 15	5 0	10 15	5 0
9	R	0 0	0 0	0 2,5	0 15ˆ	0 35ˆ	0 5	0 0	10 15	15 20	5 5	0 5
	S	0 0	0 0	2,5 7,5	15 10	35 30	5 5	0 0	15 12,5	20 17,5	5 5	0 0
Sham First												
2	S	0 0	5 10	5 10	5 12,5	5 10	0 2,5	0 2,5	5 15*	0 10ˆ	5 10	0 10
	R	0 20ˆ	30 50**	10 37ˆ	12,5 47**	10 22,5	2,5 5	2,5 5	15 45ˆ	10 27**	10 10	10 20
4	S	0 0	0 0	2,5 0	0 55ˆ	2,5 10	0 0	0 0	5 10	15 20	5 10	5 10
	R	0 0	10 35ˆ	0 15ˆ	55 77,5ˆ	10 62,5ˆ	0 0	0 0	10 82ˆ	20 25	20 25	10 17,5
6	S	0 0	0 0	0 0	0 20ˆ	0 5	0 0	0 0	0 5	0 5	0 0	0 0
	R	0 0	0 0	0 0	20 92,5ˆ	10 67,5ˆ	0 0	0 0	10 10	5 7,5	0 0	0 0
8	S	0 0	0 0	0 0	5 10	5 10	5 2,5	0 0	5 10	5 5	5 10	5 10
	R	0 0	0 0	0 32,5ˆ	22,5 50ˆ	32,5 45	2,5 0	0 0	10 10	5 5	10 17,5	10 10
10	S	0 0	0 0	0 0	0 0	0 5	0 0	0 0	0 2,5	0 0	0 0	0 0
	R	0 0	0 0	0 0	0 5	5 20**	0 0	0 0	2,5 0	0 5	0 0	0 0

Legend: P = Participants; C = Conditions; PICTDESC = Picture Description; Verb N = Verb Naming; Noun N = Noun Naming; W Repet = Word Repetition; NW Repet = Nonword Repetition; Writ N = Written Noun Naming; Writ V = Written Verb Naming; W/NW Read = Word/Nonword Reading; W/NW Dict = Word/Nonword under Dictation; S = Sham; R = Real stimulation; *= $p < 0.05$; **=$p < 0.01$; ˆ=$p < 0.001$.

influence not only on treated items but also on untreated ones of the language examination test. Interestingly, these data very much resemble those of our previous published results performed on two different groups of patients which underwent the same language treatment but combined with bihemispheric tDCS [8,9]. Since these patients were all nonfluent aphasics with severe AOS disorders [8,9] and shared the same clinical characteristic of our tsDCS group, in the next experiment, we wanted to investigate if the two techniques would result equally efficacious for improving apraxia of speech. Thus, we compared the tsDCS results with the results collected in two subgroups of patients from our previous published studies (N = 5 from each study) [8,9] who were called back again in order to perform a new study.

4. tDCS vs. tsDCS comparison

4.1. Participants

The experiment included ten participants whose clinical characteristics were the same as the tsDCS group. Patients were part of two subgroups (N = 5 for each subgroup) from our previously published tDCS studies [8,9] but they were called back again in order to perform a new experiment. Details of the ten patients have been reported previously [for details see 8,9]. All patients had nonfluent speech. Subjects were not able to produce any words in spontaneous speech. Their language production was limited to a few syllables due to their apraxia of speech disorder.

4.2. Procedure

4.2.1. Bihemispheric transcranial direct current stimulation

Transcranial direct current stimulation was applied using a battery driven Eldith (NeuroConn GmbH, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the ipsilesional and the cathode over the contralesional IFG (F5 and F7 of the extended International 10–20 system for EEG electrode placement). For sham stimulation, the same electrode positions were used. In both conditions, patients underwent concurrent speech therapy for their apraxia of speech disorder.

4.3. Procedure

The materials, the experimental procedure and the language treatment were the same as in the tsDCS experiment.

5. Results

5.1. Data analysis

Data were analysed with SPSS 17.0 software. The outcome for each group was the mean percentage of correct responses. A three-way mixed analysis of variance (ANOVA) with one between-subjects factor [GROUP (spinal vs. bihemispheric)] and two within-subjects factors [CONDITIONS (anodal vs. sham) and TIME (baseline (T0) vs. last day (T5) vs. follow up (FU)] was performed. The post-hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of p = < 0.05 were considered statistically significant.

5.1.1. Syllables

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. sham, F (1,18) = 52,70, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 52,95, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 10,72, P = .000), but the interaction GROUP*TIME*CONDITION was not significant (F (2,36) = 0.12, P = 0.89). In particular, for both groups, the Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 33 % vs. sham spinal 33 %, P = 1; anodal cortical: 37 % vs. sham cortical: 31 % P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 56 % vs. sham spinal 37 %, P = .006; anodal cortical 72 % vs. sham cortical 46 %, P = .002) and persisted at F/U (anodal spinal 51 % vs. sham spinal 30 %, P = .005; anodal cortical 67 % vs. sham cortical 44 % P = .006).

5.1.2. *Words*

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. sham, F (1,18) = 36,39, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 49,88, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 14,86, P = .000) but the interaction GROUP*TIME* CONDITION was not significant (F (2,36) = 1.73, P = 0.19). In particular, for both groups, the Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 35 % vs. sham spinal 38 %, P = 1; anodal cortical: 36 % vs. sham cortical: 29 % P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 65 % vs. sham spinal 41 %, P = .002; anodal cortical 66 % vs. sham cortical 42 %, P = .000) and persisted at F/U (anodal spinal 54 % vs. sham spinal 30 %, P = .003; anodal cortical 60 % vs. sham cortical 43 % P = .001).

5.1.3. *Sentences*

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. Sham, F (1,18) = 41,06, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 45,40, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 15,43, P = .000), but the interaction GROUP*TIME* CONDITION was not significant (F (2,36) = 0,02 P = 0.98). In particular, for both groups, the Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 10 % vs. sham spinal 10 %, P = 1; anodal cortical: 3% vs. sham cortical: 1% P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 50 % vs. sham spinal 20 %, P = .008; anodal cortical 44 % vs. sham cortical 15 %, P = .000) and persisted at F/U (anodal spinal 40 % vs. sham spinal 20 %, P = .03; anodal cortical 35 % vs. sham cortical 11 % P = 0.000) (see Fig. 4).

6. Discussion

The aim of this study was to investigate whether tsDCS would improve speech articulation in a group of ten chronic aphasic patients with concurrent AOS. At the end of treatment, results showed that only after anodal tsDCS articulatory errors significantly decreased for the treated stimuli (syllables, words and sentences). Moreover, this improvement also persisted at one week after the treatment (F/U) and generalized to the language test. Indeed, most of the patients showed significant changes in different oral language tasks (noun and verb naming, word and non-word repetition, word and non-word reading) administered before and after the treatment. No significant changes were found before and after the treatment in writing (see Table 2). This specificity argues against an effect simply due to enhanced cognitive arousal which should have influenced both oral and written tasks.

Thus, after anodal tsDCS, most patients showed a progressive reduction of phonological distortions in different oral tasks, the reduction being due to improvement in AOS. Interestingly, as also noted in our previous tDCS works [8,9], only anodal stimulation produced significant changes. Indeed, the language treatment alone did not produce significant improvement in the sham condition. This result could be ascribed primarily to the severity and chronicity of the articulatory deficit present in all patients, which is in itself particularly resistant to change [14, 17,18,64]. Indeed, since the treatment of AOS requires to plan intensive language training with repetitiveness of the exercises, it could be hypothesized that in the sham condition five days of language training were insufficient to improve performance. However, interestingly, the same amount of treatment associated with anodal tsDCS over the same time period exerted beneficial effects. Thus, similarly to previous results [8,9], combining stimulation with language training boosted language recovery overcoming the difficulties caused by the severity of the deficit. These findings are, thus, very promising as five days of tsDCS produced beneficial effects that were not achieved in the absence of stimulation.

To date, a growing body of evidence has already suggested that the neurostimulation provided by tDCS might enhance the effects of traditional language treatments for people with aphasia [41,42]. With regard

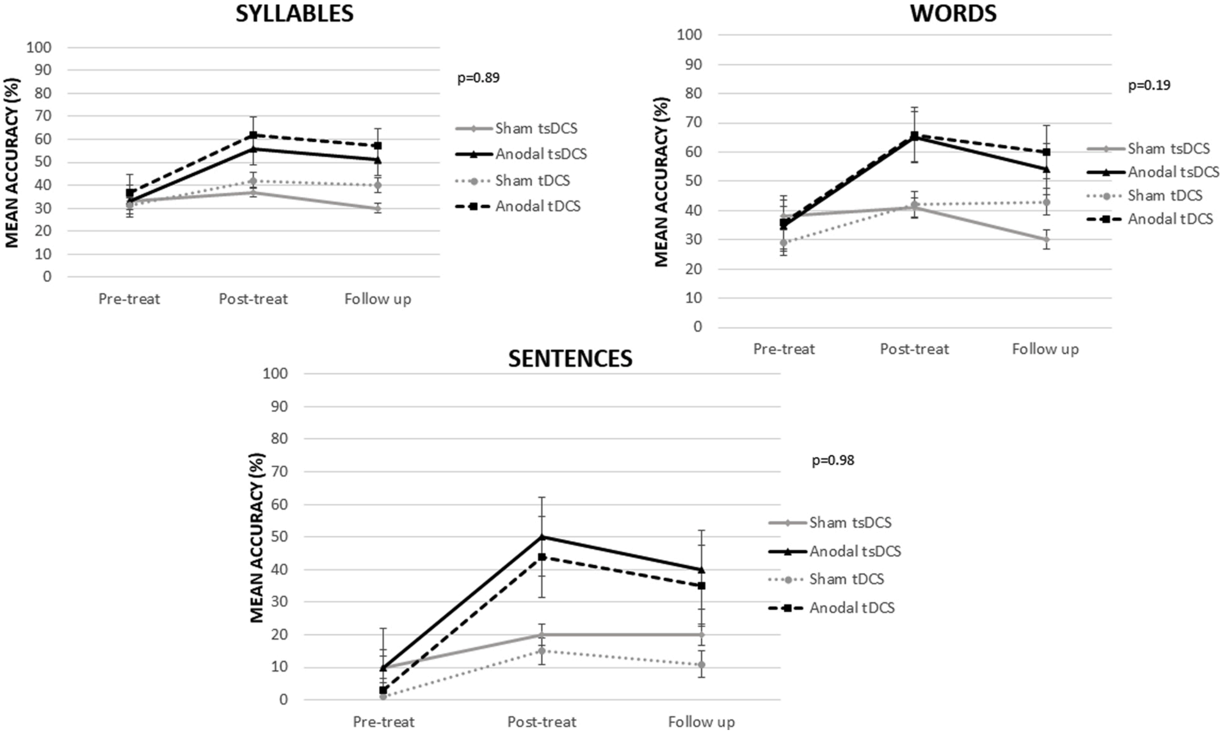

Fig. 4. Mean percentage of response accuracy for syllables, words and sentences at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition in the tDCS and tsDCS group, respectively.

to AOS, previous tDCS studies have already been proven effective in improving speech articulation in post-stroke chronic aphasia [8,9]. In particular, bihemispheric tDCS with simultaneous excitatory stimulation to the left Broca's area and inhibitory current over the right homologous improved articulatory performance in a group of aphasic individuals [8,9]. Interestingly, these effects significantly correlated with functional connectivity changes which were most pronounced in the left perilesional cortex [9]. In particular, since the behavioural treatment was focused on the motor aspects of speech production, significant changes were found in regions related to planning, maintenance, and execution of speech, such as the left premotor cortex, the left supplementary motor area and the cerebellum [9]. Thus, the results of this study revealed the activation of different sensorimotor structures involved in speech articulation confirming that articulatory processing is related to motor activity [1–3,13].

As stated in the Introduction, to date, a growing body of evidence has suggested that spinal stimulation exerts supraspinal changes by specifically influencing cortical regions, such as the sensorimotor cortices [44,45,47]. Modelling studies have further supported this issue confirming that the current delivered over the spinal thoracic vertebrae, by increasing somatosensory activity from the spinal cord to the brain, induces neurophysiological changes over the cortex [49,50]. Accordingly, in a very recent rs-fMRI study, Schweizer and co-workers [51] have shown that anodal tsDCS resulted in connectivity changes into the somatosensory cortices. Similarly, Marangolo and collaborators [52] have reported a significant correlation between the amount of verb improvement found after anodal tsDCS and supraspinal functional changes into the motor network.

Thus, given that speech articulation involves the activation of motor plans [28–34] and that tsDCS induces changes into the motor cortex [44,45,52], we might expect that in our study tsDCS would have influenced activity into the sensorimotor networks resulting efficacious for AOS recovery, which was the case.

Therefore, it could be hypothesized that either directly delivering the current over the frontal cortex through bihemispheric tDCS [8,9] or influencing the sensorimotor network in a bottom-up manner through spinal cord stimulation [44,45,52] would result equally effective for the recovery of AOS. Indeed, a direct comparison of the results obtained in the tsDCS group with those collected in the bihemisperic tDCS group, revealed no differences between the two techniques. Thus, spinal stimulation resulted efficacious as cortical stimulation.

Even if the exact underlying tsDCS mechanisms over the corticospinal system, in our study, remain largely speculative, in line with previous suggestions [65,66], the hypothesis might be advanced that anodal tsDCS has decreased the excitability of cortical inhibitory interneurons in the motor cortex, thus improving the efficacy of their correspondent areas. Indeed, while anodal tDCS is generally facilitatory to the cortex [67–69], it has been suggested that anodal tsDCS exerts inhibition due to a hyperpolarization of the axons running along the spinal columns [48,70]. An effect of tsDCS on neurotransmitters cannot also be ruled out. For instance, neurotransmitters such as GABA and glutamate undergo substantial changes after cortical tDCS over the motor cortex [71,72]. Although this effect might be task specific, one further hypothesis might be that, in our study, the inhibitory current delivered through anodal tsDCS has decreased both GABA and glutamate levels into the sensorimotor cortices leading to an improvement of their function [71–73]. According to previous hypothesis [74], we cannot also rule out the possibility that anodal tsDCS has induced an interhemispheric delay in motor connectivity, thus, enhancing the functionality of the left sensorimotor cortices through inhibition of its right homologs [74]. Indeed, the model of interhemispheric interaction (similar to models of motor recovery after stroke) suggests that, after a left hemisphere damage to the language areas, the homotopic right hemisphere regions could result abnormally activated and, thus, might exert an inhibitory effect over the residual left language area [75,76]. In this way, improvement could be possible either by stimulating the left-damaged hemisphere [77–79] or inhibiting the right contralesional areas [80–82]. Thus, the hypothesis could also be advanced that tsDCS has inhibited the motor regions of the right hemisphere increasing activity of the left correspondent areas which in turn facilitated speech articulation.

In summary, since the two techniques, in our study, yield the same results, we might suggest that, due to the ease with which tsDCS can be applied over the spinal cord, tsDCS might represent a valid new tool for the recovery of language in aphasia, at least for those aspects related to motor processing, such as action verbs and speech articulation. Indeed, current theories postulate that the language function, among which articulatory planning, is subserved by a large network of regions widely distributed across the brain [83–85]. It has also been recently suggested that a wide circuitry of distributed left motor cortical areas can be modulated by tsDCS [52]. Thus, differently from previous tDCS paradigms [42], we might hypothesized that tsDCS could result easier to use than tDCS for those language units which carry motor information, because an appropriate positioning of the anode over the spinal cord would remove the need to establish in advance which part of the sensorimotor system should be specifically targeted with DCS. Given that aphasic people, very frequently, report difficulties in verb production and/or articulatory deficits which dramatically impact the ability to produce informative speech and its intelligibility, if our results will be further confirmed in the future, we believe that tsDCS might be considered as a suitable method for the recovery of these deficits.

7. Conclusion

We are aware that our study has some limitations, the major ones are represented by the small samples of participants included and the lack of longitudinal follow-ups. Indeed, despite previous works that have been already published, due to the above reported limitations, there is still conflicting evidence for the efficacy of tDCS in post-stroke aphasia. However, considered all of these limitations, we believe that our study provides preliminary suggestions that spinal stimulation might be considered a new approach for language recovery

Funding resources

None.

CRediT authorship contribution statement

Francesca Pisano: Methodology, Formal Analysis, writing - original draft. **Carlo Caltagirone:** Project administration. **Chiara Incoccia:** Data curation. **Paola Marangolo:** Conceptualization, Writing - review & editing

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] W.J.M. Levelt, A. Roelofs, A.S. Meyer, A theory of lexical access in speech production, Behav. Brain Sci. 22 (1999) 1–75, https://doi.org/10.1017/S0140525X99001776.

[2] M. McNeil, D. Robin, R. Schmidt, Apraxia of speech: definition, differentiation, and treatment, in: M. McNeil (Ed.), Clinical Management of Sensorimotor Speech Disorders, Thieme, New York, NY, 1997, pp. 311–344.

[3] K.A. Spencer, M.A. Rogers, Speech motor programming in hypokinetic and ataxic dysarthria, Brain Lang. 94 (2005) 347–366, https://doi.org/10.1016/j.bandl.2005.01.008.

[4] E. Kearney, F.H. Guenther, Articulating: the neural mechanisms of speech production, Lang. Cogn. Neurosci. 34 (2019) 1214–1229, https://doi.org/10.1080/23273798.2019.1589541.

[5] E. Maas, D.A. Robin, D.L. Wright, K.J. Ballard, Motor programming in apraxia of speech, Brain Lang. 106 (2008) 107–118, https://doi.org/10.1016/j.bandl.2008.03.004.

[6] N.F. Dronkers, J. Ogar, S. Willock, D.P. Wilkins, Confirming the role of the insula in coordinating complex but not simple articulatory movements, Brain Lang. 91 (2004) 23–24, https://doi.org/10.1016/j.bandl.2004.06.016.

[7] A.E. Hillis, M. Work, P.B. Barker, M.A. Jacobs, E.L. Breese, K. Maurer, Re-examining the brain regions crucial for orchestrating speech articulation, Brain 127 (2004) 1479–1487, https://doi.org/10.1093/brain/awh172.

[8] P. Marangolo, V. Fiori, S. Cipollari, S. Campana, C. Razzano, M. Di Paola, G. Koch, C. Caltagirone, Bihemispheric stimulation over left and right inferior frontal region enhances recovery from apraxia of speech in chronic aphasia, Eur. J. Neurosci. 38 (2013) 3370–3377, https://doi.org/10.1111/ejn.12332.

[9] P. Marangolo, V. Fiori, U. Sabatini, G. De Pasquale, C. Razzano, C. Caltagirone, T. Gili, Bilateral transcranial direct current stimulation language treatment enhances functional connectivity in the left hemisphere: preliminary data from aphasia, J. Cogn. Neurosci. 28 (2016) 724–738, https://doi.org/10.1162/jocn_a_00927.

[10] R.T. Wertz, L.L. LaPointe, J.C. Rosenbek, Apraxia of speech: the disorder and its management, Grune Strat. (1984), https://doi.org/10.1016/j.apmr.2014.02.013.

[11] J. Ogar, H. Slama, N. Dronkers, S. Amici, M.L. Gorno-Tempini, Apraxia of speech: an overview, Neurocase 11 (2005) 427–432, https://doi.org/10.1080/13554790500263529.

[12] K. Knollman-Poter, Acquired apraxia of speech: a review, Top. Stroke Rehabil. 15 (2008) 484–493, https://doi.org/10.1310/tsr1505-484.

[13] F.L. Darley, A.E. Aronson, J.R. Brown, Motor Speech Disorders, Saunders, Philadelphia, 1975.

[14] M.R. McNeil, P. Doyle, J. Wambaugh, Apraxia of Speech: A Treatable Disorder of Motor Planning and Programming, 2000, pp. 221–266.

[15] J. Duffy, Motor Speech Disorders: Substrates, Differential Diagnosis, and Management, Elsevier Mosby, St.Louis, Mo, 2005.

[16] J.C. Rosenbek, M.L. Lemme, M.B. Ahern, E.H. Harris, R.T. Wertz, A treatment for apraxia of speech in adults, J. Speech Hear. Disord. 38 (1973) 462–472, https://doi.org/10.1044/jshd.3804.462.

[17] J.L. Wambaugh, A summary of treatments for apraxia of speech and review of replicated approaches, Semin. Speech Lang. 23 (2002) 293–308, https://doi.org/10.1055/s-2002-35802.

[18] T.R. Knock, K.J. Ballard, D.A. Robin, R.A. Schmidt, Influence of order of stimulus presentation on speech motor learning: a principled approach to treatment for apraxia of speech, Aphasiology 14 (2000) 653–668, https://doi.org/10.1080/026870300401379.

[19] A. Flinker, A. Korzeniewska, A.Y. Shestyuk, P.J. Franaszczuk, N.F. Dronkers, R. T. Knight, N.E. Crone, Redefining the role of broca's area in speech, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 2871–2875, https://doi.org/10.1073/pnas.1414491112.

[20] G. Hickok, D. Poeppel, Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language, Cognition. 92 (2004) 67–99, https://doi.org/10.1016/j.cognition.2003.10.011.

[21] E. Baker, K. Croot, S. McLeod, R. Paul, Psycholinguistic models of speech development and their application to clinical practice, J. Speech Lang. Hear. Res. 44 (2001) 685–702, https://doi.org/10.1044/1092-4388(2001/055).

[22] S. Rvachew, F. Brosseau-Lapré, Developmental Phonological Disorders: Foundations of Clinical Practice, plural publishing, San diego, ca, 2012.

[23] G.S. Dell, F. Chang, Z.M. Griffin, Connectionist models of language production: lexical access and grammatical encoding, Cogn. Sci. 23 (1999) 517–542.

[24] J.A. Coady, J.L. Evans, Uses and interpretations of non-word repetition tasks in children with and without specific language impairments (SLI), Int. J. Lang. Commun. Disord. 43 (2008) 1–40, https://doi.org/10.1080/13682820601116485.

[25] L.D. Shriberg, H.L. Lohmeier, T.F. Campbell, C.A. Dollaghan, J.R. Green, C. A. Moore, A nonword repetition task for speakers with misarticulations: the Syllable Repetition Task (SRT), J. Speech Lang. Hear. Res. 52 (2009) 1189–1212, https://doi.org/10.1044/1092-4388(2009/08-0047).

[26] D.J. Bailey, M. Blomgren, C. Delong, K. Berggren, J.L. Wambaugh, Quantification and systematic characterization of stuttering-like disfluencies in acquired apraxia of speech, Am. J. Speech-Lang. Pathol. 26 (2017) 641–648, https://doi.org/10.1044/2017_AJSLP-16-0108.

[27] J.P. Mohr, M.S. Pessin, S. Finkelstein, H.H. Funkenstein, G.W. Duncan, K.R. Davis, Broca aphasia: pathologic and clinical, Neurology 28 (1978) 311–324, https://doi.org/10.1212/wnl.28.4.311.

[28] D. Moser, J. Fridriksson, L. Bonilha, E.W. Healy, G. Baylis, J.M. Baker, C. Rorden, Neural recruitment for the production of native and novel speech sounds, Neuroimage 46 (2009) 549–557, https://doi.org/10.1016/j.neuroimage.2009.01.015.

[29] S. Jonas, The supplementary motor region and speech emission, J. Commun. Disord. 14 (1981) 349–373, https://doi.org/10.1016/0021-9924(81)90019-8.

[30] K.A. Josephs, J.R. Duffy, E.A. Strand, J.L. Whitwell, K.F. Layton, J.E. Parisi, M. F. Hauser, R.J. Witte, B.F. Boeve, D.S. Knopman, D.W. Dickson, C.R. Jack, R. C. Petersen, Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech, Brain 129 (2006) 1385–1398, https://doi.org/10.1093/brain/awl078.

[31] K.A. Josephs, J.R. Duffy, E.A. Strand, M.M. MacHulda, M.L. Senjem, A.V. Master, V.J. Lowe, C.R. Jack, J.L. Whitwell, Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech, Brain 135 (2012) 1522–1536, https://doi.org/10.1093/brain/aws032.

[32] J. Graff-Radford, D.T. Jones, E.A. Strand, A.A. Rabinstein, J.R. Duffy, K.A. Josephs, The neuroanatomy of pure apraxia of speech in stroke, Brain Lang. 129 (2014) 43–46, https://doi.org/10.1016/j.bandl.2014.01.004.

[33] A. Basilakos, C. Rorden, L. Bonilha, D. Moser, J. Fridriksson, Patterns of poststroke brain damage that predict speech production errors in apraxia of speech and aphasia dissociate, Stroke 46 (2015) 1561–1566, https://doi.org/10.1161/STROKEAHA.115.009211.

[34] R. Itabashi, Y. Nishio, Y. Kataoka, Y. Yazawa, E. Furui, M. Matsuda, E. Mori, Damage to the left precentral gyrus is associated with apraxia of speech in acute stroke, Stroke 47 (2016) 31–36, https://doi.org/10.1161/STROKEAHA.115.010402.

[35] H. Terband, B. Maassen, F.H. Guenther, J. Brumberg, Computational neural modeling of speech motor control in childhood apraxia of speech (CAS), J. Speech Lang. Hear. Res. 52 (2009) 1595–1609, https://doi.org/10.1044/1092-4388(2009/07-0283).

[36] H. Terband, B. Maassen, F.H. Guenther, J. Brumberg, Auditory-motor interactions in pediatric motor speech disorders: neurocomputational modeling of disordered development, J. Commun. Disord. 47 (2014) 17–33, https://doi.org/10.1016/j.jcomdis.2014.01.001.

[37] G. Hickok, C. Rogalsky, R. Chen, E.H. Herskovits, S. Townsley, A.E. Hillis, Partially overlapping sensorimotor networks underlie speech praxis and verbal short-term memory: evidence from apraxia of speech following acute stroke, Front. Hum. Neurosci. 8 (2014) 649, https://doi.org/10.3389/fnhum.2014.00649.

[38] J.P. Lefaucheur, A. Antal, S.S. Ayache, D.H. Benninger, J. Brunelin, F. Cogiamanian, M. Cotelli, D. De Ridder, R. Ferrucci, B. Langguth, P. Marangolo, V. Mylius, M.A. Nitsche, F. Padberg, U. Palm, E. Poulet, A. Priori, S. Rossi, M. Schecklmann, S. Vanneste, U. Ziemann, L. Garcia-Larrea, W. Paulus, Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS), Clin. Neurophysiol. 128 (2017) 56–92, https://doi.org/10.1016/j.clinph.2016.10.087.

[39] G. Schlaug, V. Renga, D. Nair, Transcranial direct current stimulation in stroke recovery, Arch. Neurol. 65 (2008) 1571–1576, https://doi.org/10.1001/archneur.65.12.1571.

[40] G. Schlaug, S. Marchina, C.Y. Wan, The use of non-invasive brain stimulation techniques to facilitate recovery from post-stroke aphasia, Neuropsychol. Rev. 21 (2011) 288–301, https://doi.org/10.1007/s11065-011-9181-y.

[41] J. Fridriksson, C. Rorden, J. Elm, S. Sen, M.S. George, L. Bonilha, Transcranial direct current stimulation vs sham stimulation to treat aphasia after stroke: a randomized clinical trial, JAMA Neurol. 75 (2018) 1470–1476, https://doi.org/10.1001/jamaneurol.2018.2287.

[42] P. Marangolo, The potential effects of transcranial direct current stimulation (tDCS) on language functioning: combining neuromodulation and behavioral intervention in aphasia, Neurosci. Lett. 719 (2020), 133329, https://doi.org/10.1016/j.neulet.2017.12.057.

[43] M.A. Nitsche, W. Paulus, Transcranial direct current stimulation - update 2011, Restor. Neurol. Neurosci. 29 (2011) 463–492, https://doi.org/10.3233/RNN-2011-0618.

[44] T. Bocci, D. Barloscio, M. Vergari, A. Di Rollo, S. Rossi, A. Priori, F. Sartucci, Spinal direct current stimulation modulates short intracortical inhibition, Neuromodulation 18 (2015) 686–693, https://doi.org/10.1111/ner.12298.

[45] T. Bocci, S. Marceglia, M. Vergari, V. Cognetto, F. Cogiamanian, F. Sartucci, A. Priori, Transcutaneous spinal direct current stimulation modulates human corticospinal system excitability, J. Neurophysiol. 114 (2015) 440–446, https://doi.org/10.1152/jn.00490.2014.

[46] P. Marangolo, V. Fiori, J. Shofany, T. Gili, C. Caltagirone, G. Cucuzza, A. Priori, Moving beyond the brain: transcutaneous spinal direct current stimulation in post-stroke aphasia, Front. Neurol. 8 (2017) 400, https://doi.org/10.3389/fneur.2017.00400.

[47] A. Truini, M. Vergari, A. Biasiotta, S. La Cesa, M. Gabriele, G. Di Stefano, C. Cambieri, G. Cruccu, M. Inghilleri, A. Priori, Transcutaneous spinal direct current stimulation inhibits nociceptive spinal pathway conduction and increases pain tolerance in humans, Eur. J. Pain 15 (2011) 1023–1027, https://doi.org/10.1016/j.ejpain.2011.04.009.

[48] F. Cogiamanian, F. M.Vergari, S. Pulecchi, A. Marceglia, A. Priori, Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans, Clin. Neurophysiol. 119 (2008) 2636–2640, https://doi.org/10.1016/j.clinph.2008.07.249 43.

[49] S. Fiocchi, P. Ravazzani, A. Priori, M. Parazzini, Cerebellar and spinal direct current stimulation in children: computational modeling of the induced electric field, Front. Hum. Neurosci. 10 (2016) 522, https://doi.org/10.3389/fnhum.2016.00522.

[50] M. Parazzini, S. Fiocchi, I. Liorni, E. Rossi, F. Cogiamanian, M. Vergari, A. Priori, P. Ravazzani, Modeling the current density generated by transcutaneous spinal direct current stimulation (tsDCS), Clin. Neurophysiol. 125 (2014) 2260–2270, https://doi.org/10.1016/j.clinph.2014.02.027.

[51] L. Schweizer, C.H. Meyer-Frießem, P.K. Zahn, M. Tegenthoff, T. Schmidt-Wilcke, Transcutaneous spinal direct current stimulation alters resting-state functional connectivity, Brain Connect. 7 (2017) 357–365, https://doi.org/10.1089/brain.2017.0505.

[52] P. Marangolo, V. Fiori, C. Caltagirone, C. Incoccia, T. Gili, Stairways to the brain: transcutaneous spinal direct current stimulation (tsDCS) modulates a cerebellar-cortical network enhancing verb recovery, Brain Res. 1727 (2020), 146564, https://doi.org/10.1016/j.brainres.2019.146564.

[53] K. Priftis, L. Algeri, L. Barachetti, S. Magnani, M. Gobbo, S. De Pellegrin, Acquired neurogenic foreign accent syndrome after right-hemisphere lesion with left cerebellar diaschisis: a longitudinal study, Cortex 130 (2020) 220–230, https://doi.org/10.1016/j.cortex.2020.05.019.

[54] P. Mariën, S. Keulen, J. Verhoeven, Neurological aspects of foreign accent syndrome in stroke patients, J. Commun. Disord. 77 (2019) 94–113, https://doi.org/10.1016/j.jcomdis.2018.12.002.

[55] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychologia 9 (1971) 97–113, https://doi.org/10.1016/0028-3932(71)90067-4.

[56] F. Fanzago, Test di valutazione dell'articolazione, Quad. Acta Phoniatr. Lat. (1983).

[57] P. Ciurli, P. Marangolo, A. Basso, Esame del Linguaggio (II versione), Organ. Spec. Firenze. (1996).

[58] E. De Renzi, P. Faglioni, Normative data and screening power of a shortened version of the token test, Cortex 14 (1978) 41–49, https://doi.org/10.1016/S0010-9452(78)80006-9.

[59] E. De Renzi, A. Pieczuro, L.A. Vignolo, Anonymous, Oral apraxia and aphasia, Cortex 2 (1966) 50–73.

[60] C.L. Smith, Handbook of the International Phonetic Association: A Guide to the Use of the International Phonetic Alphabet, 1999, https://doi.org/10.1017/S0952675700003894. Phonology. (2000).

[61] P.C. Gandiga, F.C. Hummel, L.G. Cohen, Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation, Clin. Neurophysiol. 117 (2006) 845–850, https://doi.org/10.1016/j.clinph.2005.12.003.

[62] N.E. O'Connell, J. Cossar, L. Marston, B.M. Wand, D. Bunce, G.L. Moseley, L.H. de Souza, Rethinking clinical trials of transcranial direct current stimulation: participant and Assessor blinding is inadequate at intensities of 2mA, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0047514.

[63] P. Marangolo, C.V. Marinelli, S. Bonifazi, V. Fiori, M.G. Ceravolo, L. Provinciali, F. Tomaiuolo, Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics, Behav. Brain Res. 225 (2011) 498–504, https://doi.org/10.1016/j.bbr.2011.08.008.

[64] J. Au, B. Katz, M. Buschkuehl, K. Bunarjo, T. Senger, C. Zabel, S.M. Jaeggi, J. Jonides, Enhancing working memory training with transcranial direct currentstimulation, J. Cogn. Neurosci. 28 (2016) 1419–1432, https://doi.org/10.1162/jocna00979.

[65] N. Lan, M.A. Nitsche, W. Paulus, J.C. Rothwell, R. Lemon, Effects of transcranial DC stimulation over the human motor cortex on corticospinal and transcallosal excitability, Exp. Brain Res. 43 (2004) 439–443, https://doi.org/10.1007/s00221-003-1800-265.

[66] A. Monti, F. Cogiamanian, S. Marceglia, R. Ferrucci, F. Mameli, S. Mrakic-Sposta, Improved naming after transcranial direct current stimulation in aphasia, J. Neurol. Neurosurg. Psychiatry 79 (2008) 451–453, https://doi.org/10.1136/jnnp.2007.14235666.

[67] V. Di Lazzaro, F. Ranieri, P. Profice, F. Pilato, P. Mazzone, F. Capone, Transcranial direct current stimulation effects on the excitability of corticospinal axons of the human cerebral cortex, Brain Stimul. 6 (2013) 641–643, https://doi.org/10.1016/j.brs.2012.09.006.

[68] V. Di Lazzaro, P. Profice, F. Ranieri, F. Capone, M. Dileone, A. Oliviero, I-wave origin and modulation, Brain Stimul. 5 (2012) 512–525, https://doi.org/10.1016/j.brs.2011.07.008.

[69] M. Nitsche, A. Seeber, K. Frommann, C.C. Klein, C. Rochford, M.S. Nitsche, Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex, J. Physiol. 568 (2005) 291–303, https://doi.org/10.1113/jphysiol.2005.092429.

[70] F. Cogiamanian, M. Vergari, E. Schiaffi, S. Marceglia, G. Ardolino, S. Barbieri, Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings, Pain 152 (2011) 3705, https://doi.org/10.1016/j.pain.2010.10.041.

[71] C.J. Stagg, J.G. Best, M.C. Stephenson, J. O'Shea, M. Wylezinska, Z.T. Kincses, Polarity-sensitive modulation of cortical neurotransmitters by tran-scranial stimulation, J. Neurosci. 29 (2009) 5202–5206, https://doi.org/10.1523/JNEUROSCI.44328.2009.

[72] C.J. Stagg, V. Bachtiar, H. Johansen-Berg, The role of GABA in humanmotor learning, Curr. Biol. 21 (2011) 480–484, https://doi.org/10.1016/j.cub.2011.01.069.

[73] S. Kim, M.C. Stephenson, P.G. Morris, S.R. Jackson, tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: a 7 T magnetic resonance spectroscopy study, Neuroimage 99 (2014) 237–243, https://doi.org/10.1016/j.neuroimage.2014.05.070.

[74] T. Bocci, M. Caleo, B. Vannini, M. Vergari, F. Cogiamanian, S. Rossi, A. Priori, F. Sartucci, An unexpected target of spinal direct current stimulation: interhemispheric connectivity in humans, J. Neurosci. Methods 254 (2015) 18–26, https://doi.org/10.1016/j.jneumeth.2015.07.012.

[75] P. Belin, P. Van Eeckhout, M. Zilbovicius, P. Remy, C. François, S. Guillaume, F. Chain, G. Rancurel, Y. Samson, Recovery from nonfluent aphasia after melodic intonation therapy: a PET study, Neurology 47 (1996) 1504–1511, https://doi.org/10.1212/WNL.47.6.1504.

[76] N. Murase, J. Duque, R. Mazzocchio, L.G. Cohen, Influence of interhemispheric interactions on motor function in chronic stroke, Ann. Neurol. 55 (2004) 400–409, https://doi.org/10.1002/ana.10848.

[77] J.M. Baker, C. Rorden, J. Fridriksson, Using transcranial direct-current stimulation to treat stroke patients with aphasia, Stroke 41 (2010) 1229–1236, https://doi.org/10.1161/STROKEAHA.109.576785.

[78] V. Fiori, M. Coccia, C.V. Marinelli, V. Vecchi, S. Bonifazi, M. Gabriella Ceravolo, L. Provinciali, F. Tomaiuolo, P. Marangolo, Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects, J. Cogn. Neurosci. 23 (2011) 2309–2323, https://doi.org/10.1162/jocn.2010.21579.

[79] V. Fiori, S. Cipollari, M. Di Paola, C. Razzano, C. Caltagirone, P. Marangolo, tDCS stimulation segregates words in the brain: evidence from aphasia, Front. Hum. Neurosci. 7 (2013) 269, https://doi.org/10.3389/fnhum.2013.00269.

[80] M.A. Naeser, P.I. Martin, M. Nicholas, E.H. Baker, H. Seekins, M. Kobayashi, H. Theoret, F. Fregni, J. Maria-Tormos, J. Kurland, K.W. Doron, A. Pascual-Leone, Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study, Brain Lang. 93 (2005) 95–105, https://doi.org/10.1016/j.bandl.2004.08.004.

[81] E.K. Kang, Y.K. Kim, H.M. Sohn, L.G. Cohen, N.J. Paik, Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area, Restor. Neurol. Neurosci. 29 (2011) 141–152, https://doi.org/10.3233/RNN-2011-0587.

[82] I.-Y. Jung, J.Y. Lim, E.K. Kang, H.M. Sohn, N.-J. Paik, The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients, Ann. Rehabil. Med. 35 (2011) 460–469, https://doi.org/10.5535/arm.2011.35.4.460.

[83] A.S. Dick, B. Bernal, P. Tremblay, The language connectome: new pathways, new concepts, Neuroscientist 20 (2014) 453–467, https://doi.org/10.1177/1073858413513502.

[84] E. Ripamonti, M. Frustaci, G. Zonca, S. Aggujaro, F. Molteni, C. Luzzatti, Disentagling phonological and articulatory processing: a neuroanatomical study in aphasia, Neuropsychologia 121 (2018) 175–185, https://doi.org/10.1016/j.neuropsychologia.2018.10.015.

[85] J. Klingbell, M. Wawrzyniak, A. Stockert, D. Saur, Resting-state functional connectivity: an emerging method for the study of language networks in post-stroke aphasia, Brain Cogn. 131 (2019) 22–33, https://doi.org/10.1016/j.bandc.2017.08.005.