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Article

Effects of tDCS on sound duration in patients with Apraxia of Speech in Primary Progressive Aphasia

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Abstract: Transcranial direct current stimulation (tDCS) over the left Inferior Frontal Gyrus (IFG) was found to improve apraxia of speech (AOS) in post-stroke aphasia, speech fluency in adults who stutter, naming and spelling in primary progressive (PPA). This paper aims to determine whether tDCS over the left IFG coupled with AOS therapy improves speech fluency in patients with PPA more than sham. Eight patients with non-fluent PPA with AOS symptoms received either active or sham tDCS, along with speech therapy for 15 weekday sessions. Speech therapy consisted of repetition of increasing syllable-length words. Evaluations took place before, immediately after, and two months post-intervention. Words were segmented into vowels and consonants and the duration of each vowel and consonant was measured. Segmental duration was significantly shorter after tDCS than sham for both consonants and vowels. tDCS gains generalized to untrained words. The effects of tDCS sustained over two months post-treatment in trained words. Taken together, these results demonstrate that the tDCS over the left IFG facilitates speech production by reducing segmental duration. The results provide preliminary evidence that tDCS can maximize efficacy of speech therapy in non-fluent PPA with AOS.

Keywords: apraxia of speech (AOS); transcranial direct current stimulation (tDCS); primary progressive aphasia (PPA); inferior frontal gyrus (IFG); sound duration; brain stimulation.

1. Introduction

Apraxia of speech (AOS) is a condition that affects oral motor speech planning and production and results in impaired speech fluency due to inhibition of the neural programming of articulation [1]. It can occur in the absence of dysarthria (i.e., a language impairment characterized by paralysis or paresis and muscular control problems) [2] and aphasia (a multimodal language impairment affecting language comprehension and production) [3,4]. Usually, AOS results from stroke, but neurodegeneration, traumatic brain injury, genetic disorders, or syndromes (usually as childhood apraxia of speech) may also trigger AOS [1,5-9].

The primary characteristics of AOS are articulatory and prosodic deficits with different degrees of severity from mild to severe [10,11]. Patients with AOS display inconsistent and non-systematic speech articulatory errors and irregular insertions, distortions, deletions, substitutions, and transpositions of sounds [12-15]. They often produce consonants with irregular voicing [16], stop consonants, such as /p/, /t/, /k/, with irregular plosive distortions and increased voice onset time (VOT) [17-19], or, fricative consonants, such as /f/, /θ/, /x/, with misplacing and/or misshaping of the active articulator, the tongue, relative to the passive articulator, a place in the palate [20]. AOS results in reduced coarticulation of adjacent sounds, a slowing down of syllable transitions, and non-canonical syllable segmentation [17]. Additionally, irregular prosody and rhythm have been reported as characteristics of the speech of patients with AOS [21], affecting lexical (e.g., stress) and post-lexical prominence patterns and tonalities.

In this study, we will refer to AOS in the context of primary progressive aphasia (PPA), a neurodegenerative condition with speech and language deficits as primary and prominent symptoms [22-24]. According to the consensus criteria for subtyping of PPA [25], AOS and agrammatism are key symptoms for identifying patients with the non-fluent Primary Progressive Aphasia (nfvPPA) variant from patients with other PPA variants. However, as agrammatism occurs without AOS in some patients [26] and in others AOS is the only symptom [27], a number of studies suggested a clinicopathological presentation of AOS as a distinct PPA variant, the Primary Progressive Apraxia of Speech (PPAOS) [28-30]. Most importantly, speech in patients with AOS is effortful, slow, and labored, manifested by longer, and consequently distorted, vowels and consonants [17,31]. Segmental duration can constitute a key diagnostic deficit of patients with AOS that distinguishes them from patients with other PPA symptoms [32]. Therefore, segmental duration is an objective and ecologically valid measure of AOS, and an excellent outcome measure to estimate the effects of treatment(s) and symptom progression.

Patients with AOS show subtle structural and functional irregularities in brain regions related to speech. Specifically, the left inferior frontal gyrus (IFG) has been associated with kinematic and sound representations of speech production [6,28,29,33,34]. Damage in left IFG, including all the areas of the frontal operculum: the posterior frontal gyrus i.e., pars opercularis (BA44), which is responsible for the cognitive selection of vocal and orofacial actions [33,35], the pre-Supplementary Motor Area (pre-SMA), which is responsible for vocalization [36], and the insula right under the left IFG, which is responsible for articulatory planning, causes AOS symptoms [11,37]. Other proximal and distal brain regions have also been associated with AOS, such as the parietal lobe [4], the basal ganglia, and the cerebellum [38].

The association of AOS symptoms to the left IFG has motivated neuromodulatory studies with transcranial Direct Current Stimulation (tDCS) that targeted this area. Specifically, in Marangolo, Marinelli, Bonifazi, Fiori, Ceravolo, Provinciali and Tomaiuolo [10], three subjects with stroke aphasia participated in a randomized double-blinded experiment that involved articulatory training in tDCS and sham conditions. Each subject participated in five consecutive daily sessions of anodic tDCS (20 min, 1 mA) and sham stimulation over left IFG. tDCS resulted in an improvement over the sham condition. Chesters, *et al.* [39] tested the effect of tDCS in adults who stuttered and found that anodal tDCS did not improved sentence reading, although, they observed a trend towards reduction of stuttering when tDCS was coupled with fluency. In a follow up study, Chesters, *et al.* [40] tested 30 individuals that stuttered, 15 had tDCS and 15 had sham and speech fluency intervention using choral and metronome-timed speech. They showed a significant fluency improvement in individuals with tDCS measured one week after the intervention compared to intervention without tDCS and that the effects of tDCS were maintained six weeks after therapy during reading but not during conversation. The studies show that tDCS may be effective in improving speech articulation in patient populations. Furthermore, the positive effects of tDCS in speech production are supported by studies that show that tDCS improves speech production in typical speakers [41]. Moreover, other studies show that tDCS can potentially improve additional language domains including verbal fluency in patients with Parkinson's disease (PD) [42], spoken naming [43-45], and written naming and spelling in PPA [46-49], suggest that tDCS can affect the acoustic properties of vowel production. To our knowledge, despite the high prevalence of AOS in PPA and in nfvPPA as presented above, there is no evidence whether tDCS may be a treatment adjuvant to speech therapy in PPA patients with AOS symptomatology.

In this study, we hypothesized that tDCS over the left IFG coupled with speech production therapy will improve AOS symptoms in patients with nfvPPA/ AOS more than sham, i.e., speech production treatment alone. We asked three questions (1) Is tDCS more effective than sham in improving sound duration in patients with nfvPPA/AOS? (2) Are tDCS effects sustainable? (3) Do tDCS effects generalize to untrained items? To answer these questions, we designed an experimental study where patients with nfvPPA/AOS received anodal tDCS over the left IFG or sham stimulation for the same duration paired with speech production in a word repetition task. Patients were evaluated three times, before treatment, immediately after treatment, and two months post-treatment. All words produced were segmented into vowels and consonants and we measured their temporal properties. As slow speech production is a distinguishing characteristic of the speech of patients with

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nfvPPA/AOS, a decrease in sound duration was considered as a therapeutic improvement corresponding to faster speech articulation.

2. Materials and methods

2.1. Study design and participants

The study had double-blind, cross over design with two phases. However, in this study, we analyzed only the first period to avoid dealing with carryover effects from one phase 1. Eight patients with nfvPPA/AOS participated in this study and were recruited from Johns Hopkins clinics and referrals from diagnostic centers. Inclusion criteria were to be native English speakers, minimum high-school education, progressive speech/language disorder diagnosis, absence of developmental or other neurogenic disorders, such as stroke; all participants gave informed consent. We included only those patients with nfvPPA and AOS symptoms. Patients received tDCS or sham for three weeks (15 sessions) and were evaluated three times: before therapy immediately after treatment, and two months post-treatment. Patients in the tDCS and sham arms were matched for initial demographic and clinical characteristics. Five participants received anodal tDCS over the left IFG and three participants received sham stimulation, both paired with speech therapy. Both the participant and the speech and language pathologist were blinded to the tDCS condition by means of pre-registered codes on the tDCS device, a Soterix Transcranial Direct Current Stimulator Clinical Trials Model 1500 [50].

2.1. Clinical Assessment

The subtyping of individuals with nfvPPA/AOS followed formal consensus criteria of PPA and was based on cognitive, speech and language testing, neurological examination, and neuroimaging [25]. Table 1 shows the demographic (e.g., age at the beginning of therapy, sex, and education) and neuropsychological evaluations for each participant. We report on patients' performance on the digit span forward and backward, a test measuring short-term and working memory, the Pyramids and Palm Trees [51], a test measuring semantic knowledge, the Boston Naming Test (BNT), a test measuring confrontational word retrieval, and the Subject-relative, Object-relative, Active, and Passive (SOAP), a test for syntactic comprehension [52]. We also report on disease progression using FTD-CDR scores for language and total severity (sum of domains) [53]. Severity scores for each domain range from normal (0) to questionable/very mild (0.5), mild (1.0), moderate (2.0), and severe (3.0). Domains included are memory, orientation, judgment and problem-solving, community affairs, home and hobbies, personal care, behavior/comportment, personality, and language [53].

Table 1 Demographic and neuropsychological data of the participants (numbers out of parenthesis in column mean, indicate the mean and in parenthesis the standard deviation). Total Severity = total severity scale from the Fronto-temporal Dementia Clinical Dementia Rating Scale [53]; FAS = The F-A-S Test, a subtest of the Neurosensory Center Comprehensive Examination for Aphasia (NCCEA) [54]; BNT (30) = Boston Naming Test [55]; SOAP Total = Subject-relative, Object-relative, Active, and Passive total score [52]; *p* values are reported from a Kruskal-Wallis rank sum test; * = significant.

	Sham				tDCS						
Participant	ABN	DAN	JJI	Mean	BIN	DRY	GSH	JBN	CDY	Mean	*p*
Education	16	16	16	16 (0)	16	16	20	20	16	18 (2.30)	.2
Gender	F	F	M	-	M	F	M	M	F	-	
Condition onset (years)	4	2.5	1.5	2.7 (1.3)	3	3.5	6	2	4	3.7 (1.48)	.2
Age at start of Therapy	54	71	78	67.67 (5.27)	65	53	68	65	74	65 (7.64)	.5.
Total Severity	4	4.5	5.5	4.67 (0.54)	2	0.5	2.5	1	1.5	1.5 (0.79)	.03*
F.A.S.	6	11	4	7 (3.51)	21	34	21	31	15	24.4 (7.86)	.02*

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Fruits, Animals, Vegetables	38	11	10	19.67 (5.32)	33	54	33	42	28	38 (10.27)	.2
Digit Span Forward	3.5	4	3.5	3.67 (0.25)	4.5	5.5	3.5	6	7	5.3 (1.35)	.09
Digit Span Backward	2	3.5	2.5	2.67 (0.54)	4.5	5	3.5	3	5.5	4.3 (1.04)	.07
Pyramids & Palm Trees	15	15	15	15(0)	15	15	15	15	15	15 (0)	1
BNT (30)	28	28	15	23.67 (6.62)	29	30	24	30	23	27 (3.4)	.3
SOAP Total (40)	30	33	27	30 (4.24)	35	37	35	33	37	35 (1.7)	.03*

2.3. Speech therapy methods

Speech therapy was delivered for 45 minutes from the beginning of the session (the first 20 minutes concurrently with tDCS or sham), and continued for another 20-25 minutes, for a total of 45 min. Evaluation took place before, immediately after, and at two months posttreatment. Speech therapy involved oral word repetition of increasingly complex words, modeled after Dabul et al.'s, standardized assessment [56]; e.g., *method*, *methodology*, *methodological*. We used ten triplets of increasing morphological complexity for trained words and ten triplets for untrained words matched for frequency, complexity, and length. The trained words were practiced at each treatment session whereas the untrained words were never practiced but were evaluated before treatment and at follow-up sessions for both tDCS and sham groups. Patients were first trained to the shorter words and when they would reach criterion (80% correct of the list of ten words) they would proceed to the list of the increased syllable. The goal was to improve volitional control of participants' articulators to produce co-articulated, intelligible speech, as well as to improve precision of articulation, speech rate, and speech fluency.

2.3. tDCS methods

Stimulation was delivered using Soterix Transcranial Direct Current Stimulator Clinical Trials Model 1500, delivered at 2mA intensity for 20 minutes for a total of 40mA per session (estimated current density 0.08 mA/cm^2). The current was transferred using electrodes attached to nonmetallic, conductive rubber electrodes covered with saline-soaked 5 × 5 cm (2.54 cm/inch) sponges covering the entire left IFG, corresponding to the F7 electrode [49,57,58], based on the electroencephalogram (EEG) 10-20 electrode position system [59]. The left IFG was co-registered to pretreatment magnetic resonance imaging scans using a fiducial marker. The cathode was placed on the right cheek of the participant. Extracephalic cathodal placement has been shown to better target the area in question (Russell, 2006). To mask the sham condition from the participants, sham stimulation involved a short electrical current at stimulation onset, ramping up for 30 seconds and then ramping down, that triggers a tingling sensation, that has been shown to blind the participant by creating the same initial sensation as in the tDCS condition [60]. In sham, to better simulate the actual tDCS condition, we had our device modified to induce a second ramp up and down of the current for 30 seconds in the middle of the stimulation (about 10 minutes post-onset). Participants were asked to report their overall pain level using the Wong-Baker FACES Pain Rating Scale (www.WongBakerFACES.org).

2.4. Acoustic Analysis

Each speech evaluation (before, immediately post-treatment and 2 months post-treatment) were recorded using an audio recorder that was placed approximately 1ft in front of the patient and the clinician. The audio recordings were converted into a 16000Hz mono wav file. All word productions were manually split to distinguish the clinician and the patient from the audio file. We segmented all individual vowels and consonants that made up each keyword as shown in Figure 1 uttered by clinicians and patients. Figure 1 shows the waveform in the upper tier for the word "methodology", this was part of the triplet *method*, *methodology*, *methodological* (see Appendix I, for the whole set of words evaluated), the spectrogram is shown under the waveform. The thin vertical lines that extend from the spectrogram to the penultimate tier indicate the boundaries of vowels and consonants. Each individual sound is denoted in the penultimate tier using the international phonetic alphabet.

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The whole word is shown in the last tier. The segmentation of vowels and consonants was conducted manually [61].

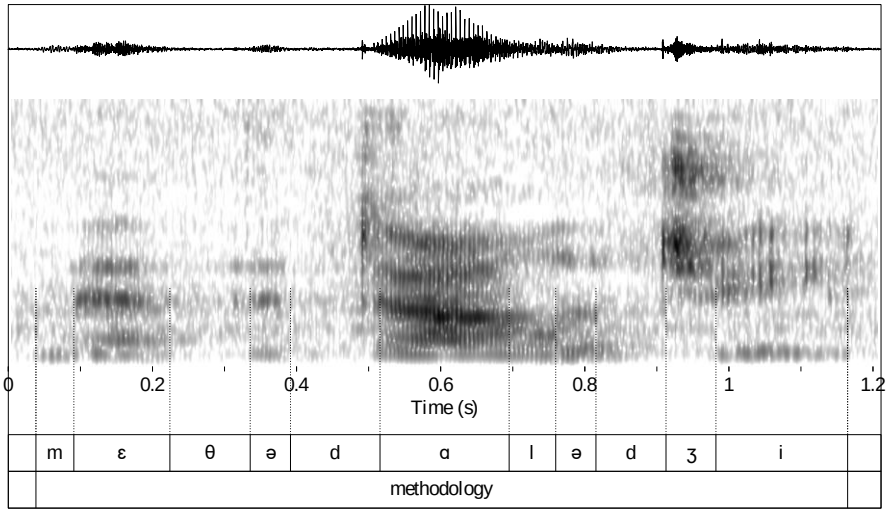

Figure 1. Waveform and spectrogram of the word *methodology* /ˌmɛθəˈdɑlədʒi/ uttered by a female patient with AOS in the nfvPPA variant. The middle tier shows with thick vertical lines the boundaries of vowels and consonants and the lower shows the target word.

The segmentation of vowels and consonants and the acoustic measurements were conducted in Praat, an acoustic analysis software [62]. From the segmented keywords, we measured the duration of each individual consonant and vowel. To compare consonant and vowel duration between patients and healthy speakers, we analyzed acoustically clinicians' productions, which they were provided as prompts in the repetition experiment.

2.6. Statistical Analysis

We designed six linear mixed effects models in R (one for trained and one for untrained items) with the duration of vowels, consonants, and the total sound duration as dependent variables and the *condition* (tDCS vs. sham) and *timepoint* (before, after, and two months post speech therapy) as predictors. To model individual differences of participants, the *participant* was modelled as a random slope. Linear mixed effects models were designed in R [63], using the "lme4: Linear Mixed-Effects Models using 'Eigen' and S4" package [64], and *p* values were calculated using the LmerTest package [65]. To compute post-hoc contrasts, we employed the R package emmeans that provides estimated marginal means (EMMs, also known as least-squares means) [66]. A *t* test was performed to compare the duration of vowels and consonants produced by patients and clinicians.

3 Results

At baseline (the before treatment timepoint) (Figure 2A), the sound duration for trained items did not differ between patients who received sham and tDCS ($t(3009)=0.4$, $p= .7$). Both tDCS and sham patient groups produced significantly longer sounds (trained and untrained) than healthy controls (i.e., the clinicians). However, immediately after treatment (Figure 2B), patients who received tDCS produced significantly shorter sounds than those who received sham ($t(2508) = 15$, $p <0.0001$), and their sound durations approximated those produced by clinicians (see Figure 2B). Importantly, patients who received tDCS maintained the tDCS gains in the 2 months post treatment follow up for trained items (see Figure 2C). Overall, tDCS resulted in significantly shorter sound durations immediately after and at 2 months post-treatment follow-ups for both trained and untrained items. We will first present the tDCS vs. sham comparison in trained (i) and untrained items (ii), and then separately for vowels (iii, iv) and consonants (v, vi).

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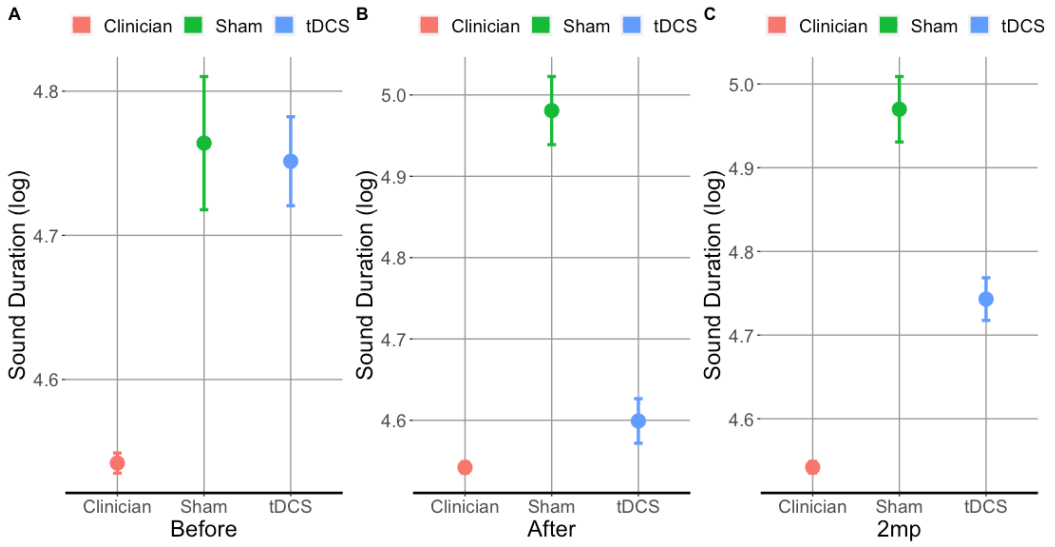

Figure 2 Vowels and consonant duration (trained and untrained) (log transformed) produced by clinicians and patients that received tDCS and sham evaluated before, error bars show 95% CI; lower values: shorter segments/faster production.

3.1 tDCS effectiveness on sound duration in trained items

The results for sound duration in the trained items are shown in Figure 3A and Table 2A. The percentage difference of tDCS vs. sham reported in the text here is calculated on the actual durational values not on the log transformed ones. At immediately after follow-up timepoint, tDCS resulted in 26% shorter than in sham sounds. This reduction in sound duration was significant as shown by the post hoc analysis using estimated marginal means (β=-0.32, *SE*=0.04, *df*=4900.5, *t*=-64.48, *p*= .0001). At the 2 months post-treatment follow-up timepoint, tDCS resulted in 29% shorter than in sham sounds (β=-0.26, *SE*=0.05, *df*=4899.01, *t*=-5.47, *p*= .0001).

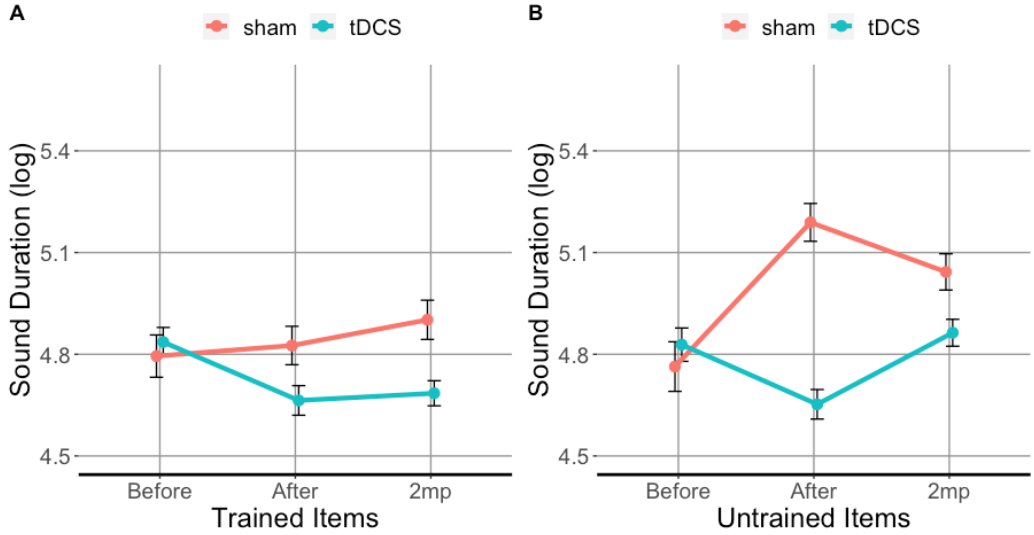

Figure 3 Trained items (panel A) and untrained items (panel B) evaluated before (before), immediately after (after), and 2 months post-treatment (2mp) for each condition. The ordinate shows the segmental (vowels and consonants) duration (log transformed), error bars show 95% CI; lower values: shorter segments/faster production. Turquoise lines show tDCS effects; red lines show sham effects.

3.2 tDCS effectiveness on sound duration in untrained items

Figure 3B and Table 2B show the results for sound duration in the untrained items. In the after period, sounds with tDCS were 47% shorter than sounds with sham (β=-0.32, *SE*=0.0493, *df*=4900.6,

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t=-6.48, *p*= .0001) and in the 2 months post intervention period, sounds with tDCS were 22% shorter than sounds with sham (*β*=-0.2559, *SE*=0.05, *df*=4899.02, *t*=-5.47, *p*= .0001).

Table 2 Linear Mixed effects models on the effects of condition (tDCS vs. sham) and period (Before, Immediately after, 2 months post treatment (2mp)) on trained (top) and untrained sound duration (bottom). The intercept of the model is the value of sham in the before phase.

			Estimate	*SE*	*df*	*t*	*p*
A.	Trained Items	Intercept	4.7955	0.1657	6.1702	28.95	< .0001
		tDCS in the After timepoint	-0.3194	0.0493	4900.5593	-6.48	< .0001
		tDCS in the 2mp timepoint	-0.2559	0.0468	4899.0188	-5.47	< .0001
B.	Untrained Items	Intercept	157.38	26.10	6.13	6.03	.0009
		tDCS in the After timepoint	-70.83	7.77	4118.15	-9.11	< .0001
		tDCS in the 2mp timepoint	-29.32	7.13	4113.91	-4.11	.00004

3.3 tDCS effectiveness on vowel duration in trained items

Figure 4A and Table 3A show the results for vowel duration in the trained items. In the after condition, vowels with tDCS were 27% shorter vowels with sham condition (*β*= -0.2434, *SE*= 0.069, *df*= 2043.05, *t*= -3.54, *p*= .001). In the 2 months post intervention, vowels with tDCS were 33% shorter than vowels with sham (*β*= -0.2820, *SE*= 0.07, *df*= 2041.63, *t*=-4.29, *p*= .001).

3.4 tDCS effectiveness on vowel duration in untrained items

Figure 4B and Table 3B show the results for vowel duration in the untrained items. In the after condition, vowels with tDCS were 55% shorter than vowels with sham. In the 2 months post therapy period, vowels were 30% shorter than vowels with sham.

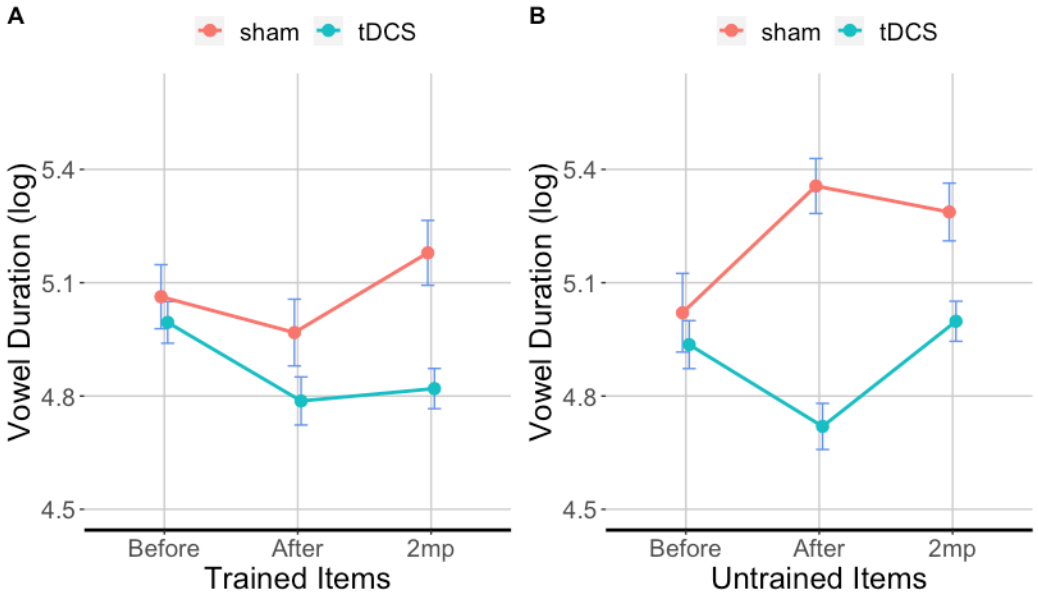

Figure 4 Trained items (panel A) and untrained items (panel B) evaluated before (before), immediately after (after), and 2 months post-treatment (2mp) for each condition. The ordinate shows vowel duration (log transformed), error bars show 95% CI; lower values: shorter segments/faster production. Turquoise lines show tDCS effects; red lines show sham effects.

Table 3 Linear Mixed effects models on the effects of condition (sham vs. tDCS) and period (Before, After, 2 months post therapy (2mp)) on trained (top) and untrained vowel duration (bottom). The intercept of the model is the value of sham in the before phase.

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		Estimate	*SE*	*df*	*t*	*p*
A. Trained Items	Intercept	5.0919	0.1728	6.3419	29.47	< .0001
	tDCS in the After timepoint	-0.2434	0.0687	2043.0476	-3.54	.0004
	tDCS in the 2mp timepointt	-0.2820	0.0657	2041.6251	-4.29	< .0001
B. Untrained Items	Intercept	5.0122	0.1740	6.3172	28.81	< .0001
	tDCS in the After timepoint	-0.6013	0.0738	1802.2565	-8.15	< .0001
	tDCS in the 2mp timepointt	-0.2455	0.0670	1797.7502	-3.66	.0002

3.5 tDCS effectiveness on consonant duration in trained items

Figure 5A and Table 4A show the results for consonant duration in the trained items. Consonants in the tDCS condition were 20% shorter than in the sham condition in the after period, and 17% shorter than sham in the 2 months post speech therapy.

3.6 tDCS effectiveness on consonant duration in untrained items

Figure 5B and Table 4B show the results for vowel duration in the untrained items. *Consonants in untrained items* that received tDCS were 36% shorter than those that received sham in the after condition and 14% shorter in the 2 months post speech therapy than consonants under sham.

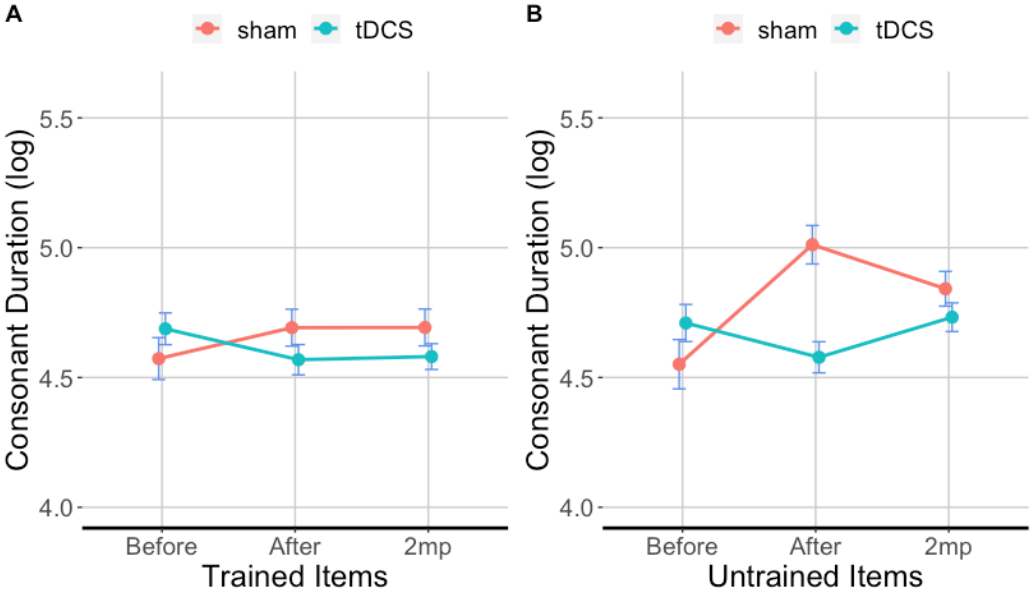

Figure 5 Trained items (panel A) and untrained items (panel B) evaluated before (before), immediately after (after), and 2 months post-treatment (2mp) for each condition. The ordinate shows consonant duration (log transformed), error bars show 95% CI; lower values: shorter segments/faster production. Turquoise lines show tDCS effects; red lines show sham effects.

Table 4 Linear Mixed effects models on the effects of condition (sham vs. tDCS) and period (Before, After, 2 months post therapy (2mp)) on trained (top) and untrained consonant duration (bottom). The intercept of the model is the value of sham in the before phase.

		Estimate	*SE*	*df*	*t*	*p*
A. Trained Items	Intercept	4.5697	0.1647	6.2897	27.75	< .0001
	tDCS in the After timepoint	-0.3307	0.0647	2804.4270	-5.11	< .0001

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	tDCS in the 2mp timepointt	-0.2239	0.0613	2803.4093	-3.65	.00027
A. Untrained Items	Intercept	4.5255	0.1897	6.1737	23.85	< .0001
	tDCS in the After timepoint	-0.5427	0.0726	2259.5804	-7.48	< .0001
	tDCS in the 2mp timepointt	-0.2540	0.0668	2255.8899	-3.80	.00015

4 Discussion

In this study, we investigated whether tDCS over the left IFG coupled with speech therapy improves sound duration in patients with nfvPPA/AOS more than sham, i.e., speech therapy alone. First, we evaluated whether tDCS is more effective than sham in improving sound duration in patients with AOS and whether effects sustained for 2 months post-treatment. Second, we evaluated whether effects were different for vowels and consonants. Furthermore, we evaluated whether the effects of tDCS generalized to untrained items. Our findings show that (1) tDCS shortens sound duration significantly more than speech therapy alone (sham). Furthermore, tDCS effects sustained over time, i.e., the tDCS advantage was maintained for up to 2 months post-treatment. (2) Patients who received tDCS coupled with speech therapy, produced shorter vowels and consonants than patients who received speech therapy alone (sham).

The most important finding of this study is that tDCS coupled with speech therapy decreased sound duration by 19% compared to sham in the after timepoint. The reduction in sound duration was significant and approached the sound duration of healthy controls, although sounds were still significantly longer from those produced by healthy controls. In sham condition, sound duration did not improve but increased slightly (1.2%) in immediately after timepoint with respect to baseline.

This study showed that combining speech training with tDCS induces more sustaining effects. Such longer lasting effects of tDCS were observed in other studies related to speech fluency and articulation. For example, Marangolo, Marinelli, Bonifazi, Fiori, Ceravolo, Provinciali and Tomaiuolo [10] in three patients with stroke-induced speech apraxia also found an improvement in response accuracy two months post-treatment. Chesters, Mottonen and Watkins [40] also showed that the tDCS effect on stuttering severity sustained for six weeks post-treatment in reading (but not in conversation). The findings of the present study suggest that tDCS combined with speech therapy inhibits the progression of AOS symptoms in patients with nfvPPA/AOS whose language deteriorates over time due to the nature of the neurodegenerative disease. Furthermore, tDCS showed significant generalization of improvement in sound duration relative to sham. Taken together our findings suggest that tDCS not only has the potential to improve AOS symptoms but this improvement may hinder the progression of the condition. This is particularly important for nfvPPA/AOS since some patients may only present with AOS symptomatology at least in initial stages [25,32]. One main reason for these findings is the stimulation over the left IFG.

We and others have shown that a possible mechanism for tDCS effects changes in functional connectivity in areas of the left IFG that control speech production [10], which resulted in an improved sound duration. Under stimulation the execution of articulatory movements and potentially articulatory planning is performed faster. Although, stimulation over the left hemisphere improved speech production, our findings do not exclude a speech improvement due to stimulation over homologue areas in the right hemisphere[67], yet current evidence favoring stimulation of the left hemisphere are stronger and supported by the results of the study.

Sound duration is sensitive to multiple effects, articulatory, and linguistic. Factors that affect duration may include articulatory planning, co-ordination, and timing of neural commands, execution of articulatory movements, control of the airflow from the lungs towards the oral cavity and the vocal fold vibration in the larynx [68-72]. Also, sound duration is sensitive to linguistic functions related to lexical stress, accentual prominence, lengthening effects demarcating the boundaries of words and phrases, speech fluency, etc. [73]. These explain why temporal properties of speech have been shown to distinguish patients with AOS from other patients PPA [8,11,32]. In other words, sound duration is better seen as an integral measure of different processes affecting speech

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production. The fact that sound duration is improved means that it could be the effect of a multidomain improvement (lung air pressure, vocal fold vibration, articulatory target approximation, etc.).

One remaining question is whether tDCS effects transfer to post-lexical coarticulation level phenomena and prosodic phenomena, such as phrasing, intonation, speech fluency, speech rate etc. that involve post-lexical processes. Future studies should plan to include language tasks, which also incorporate connected speech productions. We anticipate that an evaluation test based on connected speech can provide a broader assessment of tDCS effects on speech apraxia.

The main limitation of this study is the small number of participants and should be considered as preliminary proof-of-concept study. However, the remarkable improvement of sound duration immediately after and 2 months post treatment, shows that tDCS has the potential to enhance speech production therapy in patients with nfvPPA/AOS and warrants a larger study of tDCS over the left IFG as a therapeutic approach to improve AOS symptoms in nfvPPA/AOS.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: title, Table S1: title, Video S1: title.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, K.T. and C.T.; methodology, C.T.; software, C.T.; validation, C.T., and K.T.; formal analysis, C.T.; investigation, C.T.; resources, K.T.; data curation, K.T.; writing—original draft preparation, C.T.; writing—review and editing, C.T. and K.T.; visualization, C.T.; supervision, K.T.; project administration, K.W.; funding acquisition, K.T. All authors have read and agreed to the published version of the manuscript."

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Appendix A

Set Lists	Word Triplets		
SET 1	intervene	intervention	interventional
	progress	progression	progressive
	reflect	reflection	reflective
	stimulate	stimulation	stimulating
	stable	stabilize	stabilization
	success	successful	successfully
	excite	excitable	excitability
	improve	improvement	improving
	behave	behavioral	behaviorally
	perform	performance	performing

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SET 2	enhance	enhancement	enhancing
	suspend	suspension	suspending
	suppress	suppression	suppressive
	construct	construction	constructive
	accurate	accuracy	inaccurate
	therapy	therapeutic	therapeutically
	provide	provision	provisional
	hypothesis	hypothesize	hypothetical
	define	definition	definitive
	determine	determination	determining
SET 3	inform	information	informative
	suppose	supposition	supposedly
	restrict	restriction	restrictive
	concentrate	concentration	concentrated
	inhibit	inhibition	inhibiting
	investigate	investigation	investigator
	combine	combination	combinatory
	cognition	cognitive	cognitively
	method	methodology	methodological
	courage	courageous	encouraging

Appendix B

In addition to the quantified measurements, we have observed several co-articulatory and phonemic processes that were characteristic of these productions of individuals with nfvPPA/AOS, such as a number of phenomena that were occurring in re-occurring the speech of these individuals. Specifically, voiceless consonants were often produced as voiced before voiced nasals (e.g. encouraging /ɪnˈkʰɜrədʒɪn/ > [ɛnˈgɜːrɪdʒɪn], where the vibration of the vocal folds during the production of the nasal /n/ does not cease before the production of the adjacent voiceless consonant /k/). Voiced consonants were often produced as devoiced (*definitive* /dɪˈfɪnɪtɪv/ → [ˌtʰɪvɪnɪˈtʰɪv], aspiration results from the phonemic rule of English that aspirates onset stop consonants [74]. Overshooting or undershooting of articulatory targets related to the place of articulation (e.g. *simulation* /ˌsɪmjəˈleɪʃn/ → /ˌʃɪmjəˈleɪʃn/ an alveolar fricative sound becomes postalveolar fricative when it approaches an alveopalatal consonant). Spirantization phenomena were especially common at word codas (d → ð): method /ˈmɛːθəd/ → [ˈmɛːθəðə]. Affrication of a stop that is produced as fricative or affricate (*interventional* /ˌɪntərˈvɛnʧənəl/ → [iʰntʃʰ.ɪntʃʰɝ.ˈ væ.stɔ.nəl]). Lastrly, other coarticulatory phenomena were also observed, such as cluster simplification: (here of the /st/): stable /ˈsteɪbl/ → /ˈseɪbə/; omission: (here of the aspiration/h/): enhancement /ɛnˈhænsmənt/ → /ɛnˈæsməns/ here the articulatory command for its production fails to activate). Compensatory measures to produce lexical stress: i. longer syllable duration; ii. splitting the stressed syllable from the preceding part: excitability /ɪkˌsaɪtəˈbɪlɪti/ → [ɪkˌsaɪtə.ˈbɪlɪti]. Slow speech production and effortful speech. To explain the complex interactions between brain areas and impairment in patients with nfvPPA/AOS, cognitive models were developed for apraxia of speech often based on language models, such as those proposed by Levelt [75] and aim to describe the processes involved in apraxia modeling the invariant and variant aspects of speech production [76,77].

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