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Treatment of Primary Progressive Aphasias by Transcranial Direct Current Stimulation Combined with Language Training

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Abstract.
Background: Primary progressive aphasia (PPA) is an untreatable neurodegenerative disorder that disrupts language functions. Previous studies have demonstrated transcranial direct current stimulation (tDCS) may improve language symptoms in patients with post stroke aphasia or neurodegenerative diseases.
Objective: The present study investigated whether the application of anodal tDCS (AtDCS) to the scalp overlying the left dorsolateral prefrontal cortex (DLPFC), which may increase cortical excitability, in combination with individualized speech therapy would improve naming accuracy in the agrammatic variant of PPA (avPPA).
Methods: Sixteen avPPA patients were randomly allocated into two subgroups: AtDCS ($n = 8$) or placebo tDCS (PtDCS). tDCS was applied over the left DLPFC (BA 8/9) 25 minutes per day for two weeks (10 days). Each patient underwent 25 minutes of individualized speech therapy with either AtDCS or PtDCS during each treatment session. Neuropsychological assessment, experimental naming, and linguistic abilities in daily living were assessed at baseline (T0), after two weeks of intervention (T1) and at a 12-week follow-up (T2).
Results: Significant improvement in experimental naming was observed in both groups at T1 and T2, but this effect was significantly greater in AtDCS than PtDCS patients. Naming correctness, as assessed using the Aachener Aphasie Test, increased selectively in the AtDCS group from T0 to T1, and this effect remained significant at T2.The analysis of daily living language abilities improved selectively in AtDCS group.
Conclusion: Our results support the beneficial effect of targeted language training in combination with brain stimulation in avPPA patients. tDCS should be considered a useful tool for the improvement of language functions in patients with neurodegenerative diseases in future trials.

Keywords: Aphasia, frontotemporal dementia, non-invasive brain stimulation, rehabilitation

INTRODUCTION

Primary progressive aphasias (PPA), refer to anatomically and pathologically heterogeneous neurodegenerative disorders [1–3] that are characterized by a selective deterioration of language [4]. The canonical PPA syndromes include different entities:

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a) agrammatic variant PPA (avPPA), which is characterized by poor grammatical comprehension and expression with left dorsolateral prefrontal cortex (DLPFC) atrophy; b) semantic variant PPA, in which an impaired semantic knowledge and focal left anterior temporal lobe atrophy have been well documented; and c) logopenic variant PPA, characterized by atrophy centered in left posterior-superior temporal and inferior parietal regions and by slowed spontaneous speech output with frequent word-finding pauses and phonemic paraphasias [2]. PPA syndromes are orphaned of pharmacological or non-pharmacological interventions that reduce disease progression [2].

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) may modulate the excitability of the DLPFC circuits in order to facilitate language in older and young participant and patients with post-stroke aphasia (for a review see [5–8]).

tDCS delivers a weak polarizing electrical current to the cortex through a pair of electrodes, and brain excitability can be increased via anodal stimulation (AtDCS) or decreased via cathodal stimulation depending of the polarity of the current flow [9–11].

It has been observed that tDCS may induce improvements with respect to motor learning [12, 13], memory [14–16], perception [17], and language [18–20]. Interestingly, tDCS induces outlasting changes of cerebral excitability, thus presenting a promising tool for neuroplasticity research.

Persistent beneficial effects of tDCS have been observed in neurodegenerative and stroke patients [21–23].

Remarkably, no studies have explored the long-term effects of tDCS in avPPA patients. Using rTMS our group recently reported improved naming accuracy in avPPA patients compared to placebo stimulation [24]. However, the long-lasting effects of this treatment and potential advantages in the daily life of patients have not been demonstrated.

These observations prompted the present study, which evaluated improvements in language deficits in avPPA over time following a rehabilitative protocol.

tDCS was preferred over rTMS because this methodology was easier to use, and it can be delivered via a portable system. Either AtDCS or placebo tDCS (PtDCS) was applied randomly to the left DLPFC during individualized computerized anomia training (ICAT) for 2 weeks, and the effect of these two treatment protocols was compared at follow-up.

We hypothesized that the combined treatment (AtDCS application during ICAT) would ameliorate the language abilities that are associated with avPPA more than ICAT alone.

METHODS

Subjects

avPPA patients, who were diagnosed according to current clinical criteria [2], were enrolled from the Centre for Ageing Brain and Neurodegenerative Disorders at the University of Brescia and IRCCS Centro San Giovanni di Dio-Fatebenefratelli, Brescia, Italy.

A pool of 35 patients with avPPA was identified, and only those patients with a mild disease stage, e.g., a Frontotemporal Dementia-modified Clinical Dementia Rating scale <4 [25, 26], were invited to participate in the current study, and 16 out of 18 patients accepted.

Each patient underwent an extensive neurological and neuropsychological evaluation, a routine laboratory examination, conventional brain magnetic resonance imaging (MRI) and conventional electroencephalogram prior to entering the study to exclude potential alternative diagnoses. All patients were right-handed. All patients underwent blood sampling to screen for pathogenetic mutations within *Granulin* and *Microtuble-Associated Protein Tau* genes and detect hexanucleotide *C9orf72* expansion, as described previously [27].

Stringent exclusion criteria were applied: a) cerebrovascular disorders, previous stroke, hydrocephalus, and intracranial mass as documented by MRI; b) a history of traumatic brain injury or another neurological disease; c) significant medical problems; and d) history of seizures or implanted metal objects [10, 11, 28].

Cerebral asymmetric atrophy of the left frontotemporal lobe was an adjunctive inclusion criterion at the time of recruitment to increase the confidence of a correct diagnosis of avPPA.

Written informed consent was obtained from all subjects and responsible guardians. The local Ethics Committee approved this work and the consent procedure, in conformity with the Helsinki Declaration. The experimental methods had ethical approval from the local Human Ethics Committee (Ethics Committee of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy).

Study design

Patients were randomly assigned (1 : 1) to one of the two subgroups: 1) AtDCS plus ICAT group, in which patients received two weeks of anodal tDCS on the left

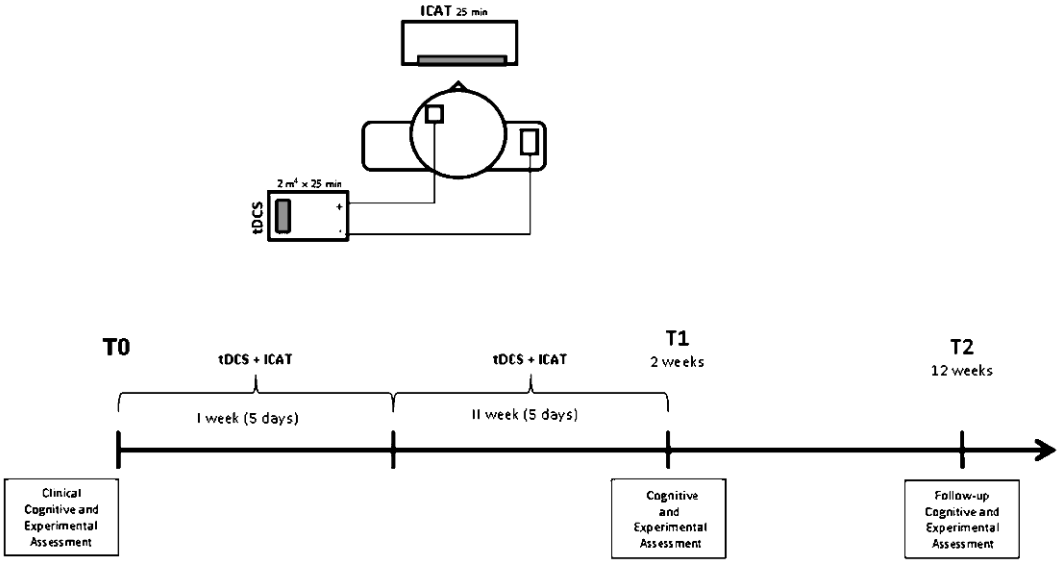

Fig. 1. Experimental therapy protocol of transcranial direct current stimulation combined with individualized computerized anomia training.

DLPFC during ICAT; and (2) PtDCS plus ICAT group, in which patients received placebo tDCS during ICAT (see Fig. 1 for the study design). All patients underwent a neuropsychological and experimental assessment before (T0), after 2 weeks of treatment (T1), and at a 12-week follow-up visit (T2).

We assessed the persistence of the effects twelve weeks (T12) from the beginning of the treatment. PPA is characterized by rapid progression that justifies a limited follow-up at 12 weeks.

Standardized neuropsychological assessment

Two trained neuropsychologists, who were blinded to patient treatment allocations (AtDCS vesus PtDCS), administered the neuropsychological testing, divided into two sessions. All of the assessments (baseline, post-treatment, and follow-ups) were administered for a single patient by the same assessor throughout the study. Linguistic abilities were analyzed using the Aachener Aphasie Test (AAT) [29], and naming and sentence comprehension subtests of the Battery for the Analysis of the Aphasic Deficit [30]. See Table 1.

Communication and functional abilities were tested using the Stroke and Aphasia Quality of Life Scale (SAQOL) [31]. The SAQOL-39 is based on four subdomains: physical, psychosocial/mood, communication, and energy. The score in each subdomain ranges from 0 (higher difficulties) to 5 (no difficulties). The Speech Questionnaire [32] and Communication Assessment Scale according to Goodglass and Kaplan were also applied [33].

Experimental naming assessment (stimuli selection)

Patients underwent two sessions of oral naming and one oral comprehension task in order to select stimuli for the therapy and assess generalization effects. Pictures for the oral naming task included 349 black-and-white drawings of objects [34]. The pictures were displayed on a computer screen using Presentation software v. 12.0. Each participant viewed black and white line drawings and named the object as accurately as possible, and oral responses were recorded and digitized at 44.1 kHz using the program GoldWave ver. 5.15.

The list of pictures was further split into two sets: the "therapy" list, which included the items to be treated (treated stimuli); and list of control stimuli, which included items not to be treated (untreated stimuli). The two lists were balanced for several variables. These two sets were further split into two balanced sub-sets for use during the first and the second weeks of treatment, respectively.

The procedure that was applied to select the "therapy" and "control" lists produced a personalized set of items for each participant, which ensured the within- and across-subject validity of the design. The accuracy in the naming of therapy and control items was

Table 1
Demographic and clinical characteristics of avPPA patients grouped according to randomized treatment procedure

Variable	avPPA all $n=16$	AtDCS group $n=8$	PtDCS group $n=8$	p-value*
Age, years	66.9 ± 8.2	63.4 ± 6.8	70.4 ± 6.8	n.s.
Gender, female	63%	63%	63%	n.s.
Age at onset, years	64.7 ± 7.6	61.4 ± 5.8	68.0 ± 5.8	n.s.
Education, years	8.2 ± 3.1	9.3 ± 3.2	7.1 ± 3.2	n.s.
Family history, positive	25%	25%	25%	n.s.
Screening for dementia				
MMSE (max = 30)	**18.3 ± 4.5**	**18.0 ± 2.9**	**18.6 ± 2.9**	n.s.
Non-verbal reasoning				
Raven-Colored Progressive Matrices (max = 36)	19.1 ± 6.4	17.6 ± 5.1	20.5 ± 5.1	n.s.
Memory				
Story Recall (max = 28)	**3.5 ± 2.2**	**3.0 ± 3.0**	**4.0 ± 3.0**	n.s.
Rey-Osterrieth Complex Figure, Recall (max = 36)	**4.4 ± 4.9**	**3.9 ± 5.5**	**4.8 ± 5.5**	n.s.
Digit Span	3.7 ± 1.2	3.6 ± 0.8	3.7 ± 0.8	n.s.
Praxia				
Rey-Osterrieth Complex Figure, Copy (max = 36)	**16.4 ± 12.2**	**14.5 ± 12.9**	**18.3 ± 12.9**	n.s.
Executive function				
Trail-Making Test A (s)	**148.6 ± 108.4**	**116.0 ± 114.1**	**177.1 ± 114.1**	n.s.
Trail-Making Test B (s)	**443.7 ± 139.1**	**419.7 ± 163.7**	**464.6 ± 163.7**	n.s.
Language				
Fluency, Phonemic	**8.9 ± 4.7**	**9.8 ± 4.1**	**8.0 ± 4.1**	n.s.
Fluency, Semantic	**11.7 ± 4.1**	**13.5 ± 4.2**	**9.9 ± 4.2**	n.s.
Aachener Aphasia Test				
Token Test, Errors, (max = 150)	**25.4 ± 7.5**	**26.5 ± 6.0**	**24.45 ± 6.0**	n.s.
Repetition (max = 150)	**127.8 ± 14.8**	**125.3 ± 13.4**	**130.3 ± 13.4**	n.s.
Writing (max = 90)	**70.3 ± 16.7**	**67.9 ± 9.8**	**72.8 ± 9.8**	n.s.
Naming (max = 120)	**85.1 ± 13.7**	**85.6 ± 16.1**	**84.5 ± 16.1**	n.s.
Comprehension (max = 120)	**92.0 ± 19.8**	**89.8 ± 8.4**	**94.3 ± 8.4**	n.s.
Battery for the Analysis of the Aphasic Deficits				
Sentence Comprehension (accuracy, %)	71.9 ± 12.9	73.3 ± 16.6	70.6 ± 16.6	n.s.
International Picture Naming Project Task				
Action naming (accuracy, %)	46.8 ± 14.0	49.5 ± 12.8	44.0 ± 12.8	n.s.
Object naming (accuracy, %)	56.6 ± 17.1	61.4 ± 21.8	51.8 ± 21.8	n.s.

*AtDCS versus PtDCS. n.s., not significant. Bold data indicate scores below cut-off. avPPA, agrammatic variant primary progressive aphasia; AtDCS, anodal tDCS; PtDCS, placebo tDCS; MMSE, Mini-Mental State Examination.

assessed at the end of the rehabilitation and during follow-up visits.

Therapy protocol

Participants received 25 minutes of speech therapy during tDCS treatment (either AtDCS or PtDCS) on a daily basis (5 days/week) and for 2 weeks. The patient was seated in front of a computer screen in a quiet room while the treatment protocol was displayed using Presentation software v. 12.0. The treatment included several steps to elicit the production of a target noun: repetition of the target word; articulatory suppression task; oral picture naming; and reading of the target word. The trial was repeated for each error [6].

tDCS

All of the patients received two weeks of tDCS stimulation over the left DLPFC (half of the patient received anodal and half of the patients received placebo stimulation) in combination with ICAT.

Referring to naming, we targeted the left DLPFC during stimulation in line with previous studies that used brain stimulation to demonstrate the involvement of this area in naming abilities in the young, in healthy elderly participants, and in patients [7, 20, 24, 35–39]. Moreover, we selected this area because avPPA patients are characterized by predominantly left-sided DLPFC atrophy and we aimed to increase the functioning of this area.

Each week of the tDCS treatment consisted of 5 sessions of 25 minutes/day (25 minutes of tDCS during 25 minutes of ICAT). The stimulation was delivered using a battery-driven constant-current stimulator (BrainStim, EMS, Bologna, Italy) through a pair of saline-soaked sponge electrodes. The active electrode (5 × 5 cm) was placed on the left DLPFC, 8 cm frontally and 6 cm laterally with respect to the scalp

vertex. The reference electrode (6 × 10 cm) was placed on the right arm.

A constant current of 2 mA was applied for 25 minutes (current density of active electrode 0.08 mA/cm^2) with a ramping period of 10 seconds at the beginning and end of the stimulation [10, 11, 28]. The current density was maintained below the safety limits [11, 28]. In the sham stimulation (i.e., placebo), the current was turned off 10 seconds after the beginning of the stimulation (plus the duration of the fade-in) and was turned on for the last 10 seconds of the stimulation period (plus the duration of the fade-out periods = 10 seconds). The patients felt the itching perceptual sensations below the electrodes at the beginning and at the end of the stimulation, making this condition indistinguishable from the experimental stimulation [40].

Statistics

The demographic variables (e.g., age and education) of the two groups were compared at baseline using parametric analyses (*t*-test).

The behavioral effects induced by the protocol after two weeks of daily stimulation and language training were assessed using a 2 (group: AtDCS plus language training versus PtDCS plus language training) × 3 (time: baseline, two weeks, 12 weeks) ANOVA. Fisher's least significant difference test was further applied.

RESULTS

Subjects

The primary demographic and clinical characteristics of avPPA patients according to treatment procedure, i.e., AtDCS ($n=8$) and PtDCS ($n=8$), are summarized in Table 1. The two treatment groups did not differ in demographic variables.

One of the 16 avPPA patients carried the *GRN Thr272fs* mutation in the AtDCS group. No other pathogenetic mutations within the examined genes were detected.

Standard neuropsychological assessment at follow-up

A significant effect of treatment was observed for the naming subtest of AAT. A significant main effect of time [F(2, 11) = 4.89, $p=0.018$, $\eta^2=0.308$] and the interaction between time and group [F(2, 22) = 3.63, $p=0.043$, $\eta^2=0.248$] was observed. Naming correctness increased selectively in the AtDCS group (T0 = 85.17 ± 6.5, T1 = 96.33 ± 6.7, $p=0.001$), and this effect remained significant from T0 to T2 (91.33 ± 5.8; $p=0.049$) (Fig. 2). The PtDCS group exhibited stable performances throughout the three assessments.

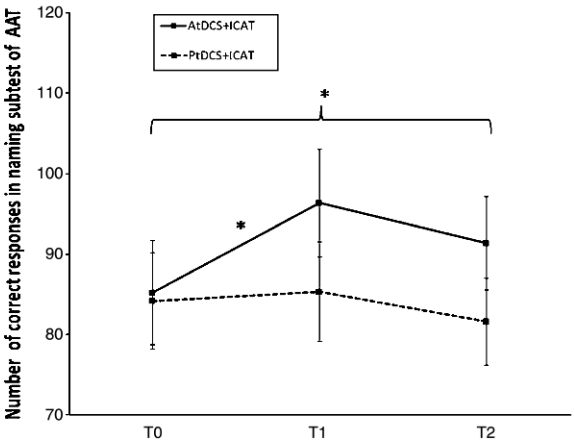

Fig. 2. Accuracy in Aachener Aphasie test (AAT) naming subtest (minimum, low performance = 0, maximum, high performance = 120) at baseline (T0) and at two (T1) and 12 (T2) weeks in avPPA patients who received AtDCS + ICAT (continuous line) or PtDCS + ICAT (dotted line) (*$p<0.05$). Error bars represent standard errors.

Experimental naming assessment

We established the baseline for the treated and the untreated lists for each patient. The percentage of correct responses at baseline for each subject corresponded to the number of items that were named correctly in 1 of the 2 naming assessment sessions, divided by two, further divided by the total number of items in the therapy and control lists (the treated and the untreated lists included the same number of items) and multiplied by 100.

Treated stimuli

A significant main effect of time [F(2, 11) = 44.27, $p=0.02$, $\eta^2=0.800$] and the interaction between timing and group [F(2, 22) = 3.70, $p=0.041$, $\eta^2=0.251$] was observed. Both groups exhibited improved naming abilities for the treated items [AtDCS, T0 = 25.6 ± 3.6, T1 = 77.2 ± 6.8, $p<0.001$; PtDCS, T0 = 24.3 ± 3.3, T1 = 54.0 ± 6.3, $p<0.001$], but a greater effect was observed at T1 in the AtDCS group compared to the PtDCS group ($p=0.020$). Interestingly, the improvement in naming abilities remained significant at

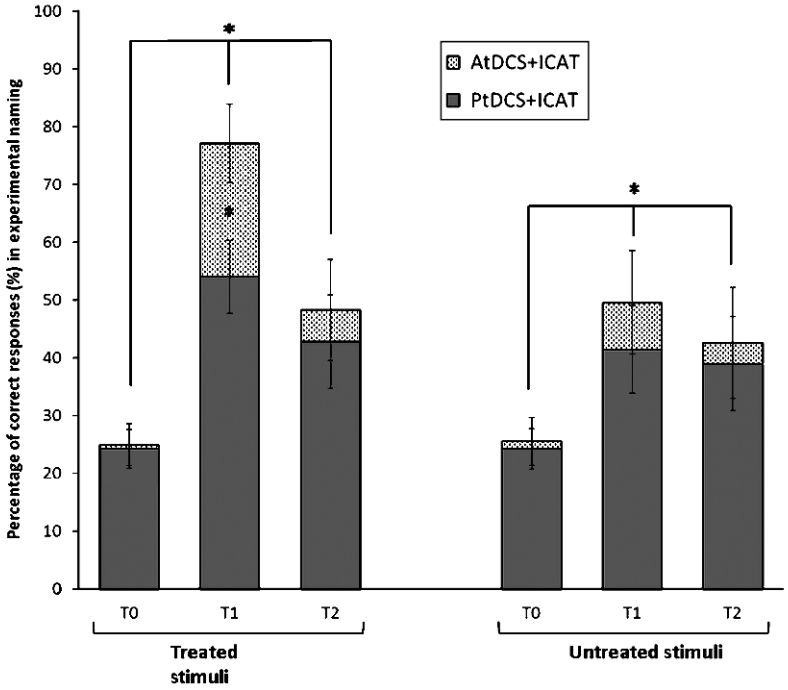

Fig. 3. Naming accuracy (%) for treated and untreated stimuli at baseline (T0) and at two (T1) and 12 (T2) weeks in avPPA patients who received AtDCS + ICAT or PtDCS + ICAT (*$p < 0.05$). Error bars represent standard errors.

T2 in both groups (AtDCS = 48.3 ± 8.7, $p = 0.001$; PtDCS = 42.9 ± 8.1, $p = 0.005$) (See Fig. 3 for details).

Untreated stimuli

A significant main effect of time [F(2, 11) = 15.48, $p < 0.001$, $\eta^2 = 0.585$] was observed with comparable improvement in both groups [AtDCS, T0 = 25.6 ± 3.6 and T1 = 49.6 ± 9.0; PtDCS, T0 = 24.3 ± 3.3 and T1 = 41.4 ± 7.6; $p = <0.001$]. Interestingly, the improvement in naming abilities remained significant at T2 (AtDCS = 42.6 ± 9.6, PtDCS = 39.0 ± 8.1, $p < 0.001$) (See Fig. 3 for details).

Treated versus untreated stimuli

We conducted two dependent *t*-tests, one for each group, to compare the magnitude of the improvement after the treatment (performance at T1-performance at T0) for the treated and untreated stimuli and investigate whether the two-week treatment induced greater effects on treated than untreated stimuli. This analysis revealed that the effect on treated stimuli was greater than the effect on untreated stimuli in the AtDCS (treated stimuli: +45.8 ± 15.8, untreated stimuli: +21.3 ± 10.5; $p = 0.013$) and PtDCS groups (treated stimuli: +34.3 ± 21.5, untreated stimuli: +20.75 ± 16.5; $p = 0.035$).

Functional communication scales

A significant group × timing interaction was observed for the energy subdomain of SAQOL [31] [F(2, 22) = 5.88, $p = 0.009$, $\eta^2 = 0.348$], which was completed by the patients. A subjective worsening was observed in the PtDCS group after two weeks of treatment (T0 = 4.06 ± 1.23 versus T1 = 3.60 ± 1.29, $p = 0.05$), and the scores did not change from T1 to T2 (3.44 ± 1.62). Conversely, an improvement from T0 to T1 was recorded in the AtDCS group, (T0 = 3.95 ± 0.96, T1 = 4.68 ± 0.61; $p = 0.043$), which did not persist at T2 (4.56 ± 0.58, T0 versus T2, $p = 0.19$).

The analysis on the production section of the Speech Questionnaire [32], which was completed by the caregiver, revealed a significant effect of timing [F(2, 11) = 5.48, $p = 0.013$, $\eta^2 = 0.354$] and a timing × group [F(2, 20) = 5.23, $p = 0.015$, $\eta^2 = 0.344$] interaction. Speech production abilities improved selectively in the AtDCS group (T0 = 10.86 ± 1.95 versus T1 = 12.86 ± 1.77, $p = 0.002$), but this effect was

Table 2
Communication abilities scales. The score ranges from 0 (higher difficulties) to 5 (no difficulties) for stroke and aphasia quality of life scale and ranges from 0 (higher difficulties) to 14 (no difficulties) for production section and from 0 (higher difficulties) to 5 (no difficulties) for comprehension section of speech questionnaire

Stroke and aphasia quality of life scale				
	Patients group	T0	T1	T2
Physical	AtDCS + ICAT	4.86 ± 0.16	4.83 ± 0.24	4.84 ± 0.15
	PtDCS + ICAT	4.77 ± 0.30	4.88 ± 0.22	4.89 ± 0.12
Communication	AtDCS + ICAT	3.53 ± 1.08	3.56 ± 1.14	3.52 ± 0.67
	PtDCS + ICAT	3.31 ± 0.99	3.20 ± 1.00	3.50 ± 1.03
Psychosocial/Mood	AtDCS + ICAT	4.14 ± 0.96	4.06 ± 1.01	4.39 ± 0.47
	PtDCS + ICAT	3.57 ± 1.11	4.02 ± 0.72	3.84 ± 1.05
Energy	AtDCS + ICAT	3.95 ± 0.96	4.68 ± 0.61*	4.56 ± 0.58
	PtDCS + ICAT	4.06 ± 1.23	3.60 ± 1.29^	3.44 ± 1.62^
Speech Questionnaire				
Production	AtDCS + ICAT	10.86 ± 1.95	12.86 ± 1.77*	10.60 ± 2.70
	PtDCS + ICAT	12.13 ± 1.25	12.38 ± 1.85	12.71 ± 1.38
Comprehension	AtDCS + ICAT	4.29 ± 1.11	4.57 ± 0.53	4.80 ± 0.45
	PtDCS + ICAT	3.50 ± 1.60	4.50 ± 0.76	3.71 ± 1.25

*Improvement as compared to baseline, $p < 0.05$. ^worsening as compared to baseline, $p < 0.05$, AtDCS, anodal tDCS; PtDCS, placebo tDCS; ICAT, individualized computerized anomia training.

not observed at T2 (10.6 ± 2.7, $p = 0.81$). The PtDCS group did not exhibit any significant changes over time (see Table 2).

Patient carrying GRN mutation

The patient who carried the *GRN* mutation exhibited improvement in the AAT naming subtest at follow-up (T0 = 77, T1 = 97, χ^2 (Yates correction) = 15.959, $p = 0.0001$). This patient also exhibited improvement in the experimental naming assessment in treated (T0 = 25%, T1 = 85%, χ^2 (Yates correction) = 70.323, $p = 0.0001$) and untreated stimuli (T0 = 25%, T1 = 50%, χ^2 (Yates correction) = 12.288, $p = 0.0005$) with a stable effect at T2 versus T0 (Treated stimuli = 45%, χ^2 (Yates correction) = 7.934, $p = 0.005$; Untreated stimuli = 50%, χ^2 (Yates correction) = 12.288, $p = 0.0005$). The patient improved in the in the energy subdomain of the SAQOL (T0 = 4, T1 = 5, T2 = 5), and in the production section of the Speech Questionnaire (T0 = 12, T1 = 14, T2 = 12).

DISCUSSION

The present study investigated whether AtDCS in combination with individualized computerized anomia training could improve naming in avPPA patients. In particular, we examined whether this combined treatment could ameliorate the language difficulties in avPPA more than anomia training alone. We also evaluated the persistence of the cognitive benefits over time.

The present results support our working hypotheses because a significant effect of combined treatment on experimental naming accuracy was observed and remained after three months. Interestingly, this result was also demonstrated using a detailed neuropsychological assessment and corroborated using functional communication scales that were administered to patients and their caregivers.

We suggest that the stimulation of left DLPFC can facilitate the lexical retrieval processes in avPPA [41]. This hypothesis is supported in a recent rTMS work from our group [24]. This study demonstrated an improvement in linguistic performance following DLPFC stimulation, in patients with avPPA. Consistently with our hypothesis, we failed to observe an effect of rTMS in patients with semantic variant PPA, in which semantic knowledge is degraded. Functional imaging studies shed light on the patterns of reorganization in the language system in PPAs [42], and strongly support changes in language network connectivity [43] and metabolism abnormalities within language networks [44]. tDCS may affect these networks and increase or decrease neuronal excitability, which modulates language task performances.

The beneficial role of tDCS has been addressed recently in different cognitive domains, such as visuospatial attention deficits in stroke patients [45], language abilities in vascular aphasias [8] and memory in Alzheimer's disease [22]. Anodal tDCS may exert its effect on cognitive performances by increasing neuronal excitability and modifying cortical plasticity, which improves cognitive functions [9, 46–49]. The present results suggest that AtDCS coupled with

anomia training promotes the long-term rearrangement of synaptic connections within language networks. This selective effect is further confirmed by the present data because we did not observe any effect on cognitive abilities other than language.

A single session of AtDCS alone, without combined cognitive training, does not affect language performance in PPA patients [50]. However, increased efficacy of daily tDCS combined with cognitive rehabilitation has been observed in patients with aphasia [21, 51–54].

Our study presents the first evidence that a combined treatment is effective for the treatment of language deficits in avPPA patients, and these cognitive effects persisted for up to 12 weeks. This effect was also observed in one case of avPPA due to genetic disease.

An important issue that requires further discussion is the generalization of therapeutic effects on treated and untreated items [55]. The improvement on treated items is expected, but the generalization to untreated items has not been recorded using different treatment approaches. Our data revealed a training-induced effect on untrained stimuli in both groups, which suggests the capacity of our individualized computerized anomia training to induce a generalization beyond the specific training stimuli and, consequently, its usefulness in the rehabilitation of naming difficulties in avPPA patients. The improvements in treated and untreated items persisted for 12 weeks, which emphasizes that the generalization to untreated stimuli was long-lasting. This generalization is likely due to language training more than tDCS because it was present in both the AtDCS and PtDCS groups.

Importantly, the experimental naming assessment and neuropsychological and functional assessments revealed differences between groups, which suggests an additional beneficial effect of the combined treatment compared to the application of a single method. Therefore, improvements in the AtDCS group in treated items of experimental naming proved the additional benefits of the combined treatment.

The strengths of the present work are supported by the careful clinical and language assessments prior to and after treatment interventions. Moreover, the improvements in language ability were observed in experimental naming assessments and formal language evaluation (AAT). We only observed improvement in the AAT and the functional communication abilities in the AtDCS group, which were assessed by the formal scales that were completed by patients and caregivers. The caregiver scales further accomplished the functional relevance of the present results in everyday life abilities.

We acknowledge that this study includes some limitations. In particular, the number of patients was relatively small, and the lack of a placebo stimulation group, without speech therapy, and a longer follow-up is required to evaluate the trajectories of progression. This latter aspect would assist the determination of whether and when an extra rehabilitation protocol should be considered over time. The inclusion of a control group receiving only individualized language treatment is required to identify the amount of contribution of the language therapy alone and in combination with tDCS treatments.

Finally, human language is a complex behavior that involves multiple processes and one important process in the constellation of language skills is naming [56]. Evidence from both lesion and imaging studies suggests a central role of the left prefrontal, temporal, and parietal areas during naming [57–59]. However, given that the size of the electrodes delivering AtDCS in the present study was 25 cm^2, the focality is rather low. With this limited spatial resolution, it cannot be ruled out that the effect of AtDCS was not exclusively attributed to the DLPFC.

Future longitudinal investigations might elucidate the treatment-specific changes and neural responses through functional imaging. To shed further light on the role of the two hemispheres in language processing in PPA, future studies might examine brain atrophy as a predictor of treatment effects. Additional evidence is necessary to identify and characterize the influence of tDCS parameters (e.g., unihemispheric versus bihemispheric) on language outcomes to characterize its role in language rehabilitation as highlighted in a recent study [60]. In conclusion, the present results suggest that tDCS coupled with ICAT is an effective treatment strategy for language disturbances in avPPA patients and supports the potential usefulness of brain stimulation as a tool for the promotion of neuroplasticity and the development of novel neurorehabilitation strategies.

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