ARTICLE CLASS OF EVIDENCE

Language boosting by transcranial stimulation in progressive supranuclear palsy

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Abstract

Objective

To explore whether transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) can improve language capacities in patients with progressive supranuclear palsy (PSP).

Methods

We used a sham-controlled double-blind crossover design to assess the efficiency of tDCS over the DLPFC in a cohort of 12 patients with PSP. In 3 separate sessions, we evaluated the ability to boost the left DLPFC via left-anodal (excitatory) and right-cathodal (inhibitory) tDCS, while comparing them to sham tDCS. Tasks assessing lexical access (letter fluency task) and semantic access (category judgment task) were applied immediately before and after the tDCS sessions to provide a marker of potential language modulation.

Results

The comparison with healthy controls showed that patients with PSP were impaired on both tasks at baseline. Contrasting poststimulation vs prestimulation performance across tDCS conditions revealed language improvement in the category judgment task following right-cathodal tDCS, and in the letter fluency task following left-anodal tDCS. A computational finite element model of current distribution corroborated the intended effect of left-anodal and right-cathodal tDCS on the targeted DLPFC.

Conclusions

Our results demonstrate tDCS-driven language improvement in PSP. They provide proof-of-concept for the use of tDCS in PSP and set the stage for future multiday stimulation regimens, which might lead to longer-lasting therapeutic effects promoted by neuroplasticity.

Classification of evidence

This study provides Class III evidence that for patients with PSP, tDCS over the DLPFC improves performance in some language tasks.

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Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **DLPFC** = dorsolateral prefrontal cortex; **FAB** = Frontal Assessment Battery; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurological Institute; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **tDCS** = transcranial direct current stimulation; **TMS** = transcranial magnetic stimulation.

Progressive supranuclear palsy (PSP) is a neurodegenerative disease damaging mainly the basal ganglia, the midbrain, and the superior cerebellar peduncle.[1] However, several studies have also reported damage to cortical regions, particularly to the dorsolateral prefrontal cortex (DLPFC).[1–3]

The clinical features of the most frequent PSP variant, the Richardson syndrome, are parkinsonism, postural instability, and impairment of vertical eye saccades.[4] In addition, various investigations have shown cognitive disorders including a breakdown of executive function and language capacities.[5,6] Regarding language, patients have impaired access to lexical and semantic representations, causing a diminution of language initiation/fluidity.[1,6–10] Accordingly, patients with PSP demonstrate impaired performance on a range of lexical/semantic tests including synonym judgment, semantic associations, single-word comprehension, naming, and word fluency tasks.[6,11,12] Neuroimaging studies in patients with PSP have demonstrated correlations between such language disorders and atrophy levels in the left DLPFC.[1,5]

Despite growing insight into the mechanisms of motor and cognitive disorders in PSP, no validated therapy is available.[13] Regarding cognitive/language deficits, several authors have explored the use of anti-Alzheimer molecules without any positive effects.[13] Similarly, speech therapy approaches have not led to any validated protocol.[14] In this context, noninvasive neurostimulation aiming at boosting cognitive/language performance in brain-damaged patients may represent a promising perspective.

Several investigations using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have shown improvement of language recovery in poststroke aphasia.[15] Capitalizing on the principle of interhemispheric inhibition[16] and under the assumption that anodal stimulation facilitates neural activity whereas cathodal stimulation inhibits it,[17] several authors have shown that left-anodal stimulation over language-related areas and right-cathodal stimulation over homotopic right-sided regions generate the most positive effects on language recovery.[15,18,19] Moreover, long-lasting effects persisting for several months after multiday stimulation regimens linked to neuroplasticity open avenues for future therapeutic applications.[19] Stimulation studies have provided evidence for improvement of language performance in neurodegenerative conditions such as Alzheimer disease[20] and primary progressive aphasias (PPA).[21–23] However, many of these investigations did not implement a double-blind or a sham-controlled design, limiting their ability to report genuine effects on language networks and performance. Recently, a double-blind sham-controlled tDCS study in the semantic variant of PPA reported improvement of semantic processing specifically in the verbal domain, following anodal and cathodal stimulation over the left and the right anterior temporal lobes, respectively.[23] Such a rigorous methodology yielding positive results paves the way to explore similar approaches in other neurodegenerative conditions with impaired language function, such as PSP.

We used a double-blind, sham-controlled, crossover design on a well-characterized cohort of patients with PSP applying single sessions of anodal and cathodal tDCS over the left and right DLPFC, respectively. Lexical and semantic access and language initiation/fluidity were evaluated with a "category judgment" and a "letter fluency" task prior to and following tDCS. To demonstrate potential language-specific improvement, we also applied a control task tapping non-language-related executive functioning.

Methods

Participants

Twelve patients with PSP were recruited at the National Reference Center for Rare Dementias and PSP, Pitié-Salpêtrière Hospital, Paris, France. The diagnosis was established by expert clinicians following international diagnostic criteria.[24] All patients had progressive disease evolution including predominantly axial parkinsonism, postural instability leading to falls during the first year of the disease, and impairment of vertical eye saccades. All patients also presented impairment of executive functions and decreased verbal fluency. Patients were included only when psychotropic medication such as antidepressant, anxiolytic, or antipsychotic drugs, or dopaminergic molecules, have been stopped at least 3 months before the inclusion to avoid any medication-induced biases of the results. Such biases were also minimized by our study design in which all patients received the 3 stimulation modalities (left-anodal/right-cathodal/sham), in a counterbalanced order permutation. Exclusion criteria were (1) psychiatric or neurologic diseases other than PSP; (2) contraindications for MRI or tDCS such as intracranial ferromagnetic devices, scalp/skull lesions, or epilepsy; and (3) major depression (Montgomery-Åsberg Depression Rating Scale [MADRS] > 20[25]) or major cognitive disorders (Mini-Mental State Examination [MMSE] < 15[26]; Frontal Assessment Battery [FAB] < 10[27]). Fifteen healthy controls were

also included to determine normative performance levels in the experimental language tasks. They were recruited via an announcement that healthy volunteers are needed for a research program, and they mostly were spouses or friends of the patients. Controls and patients with PSP had similar characteristics for handedness, sex, age, and years of education (χ^2 test for sex: $p > 0.05$; Mann-Whitney tests for age and years of education: both $p > 0.05$). All participants were native French speakers. Demographic data are summarized in table 1.

Standard protocol approvals, registrations, and patient consents

The study received approval from the local ethics committee (RCB-2013-A00734-41) and written informed consent was obtained from all participants. A clinical trial identifier number was not obligatory and not requested for this pretherapeutic proof-of-concept study.

General study design

We applied a double-blind sham-controlled crossover design in which each patient underwent 3 separate tDCS sessions: anodal and cathodal tDCS over the left and right DLPFC, respectively, and sham stimulation over the left DLPFC. To evaluate the effects of each tDCS modality, stimulation was immediately preceded and followed by experimental tasks assessing lexical and semantic access, language fluidity/initiation, and executive functions. Given that the period of offline effects of a single tDCS session is about 20–30 minutes,[28] we did not apply follow-up evaluations in this exploratory proof-of-concept study.

The order of the 3 stimulation sessions was counterbalanced across the patient cohort to avoid order biases (6 order permutations × 2 patients for each order). A computer-generated randomization list was created before the inclusions, and 12 sequentially numbered sealed envelopes containing the 12 (6 × 2) orders of the 3 stimulation sessions were saved in a research file box. Following the inclusion of a patient, the researcher responsible for the stimulation sessions opened the envelope without revealing the order information to any other person involved in the study. tDCS sessions were separated 7 days apart to prevent unlikely carryover effects.[28] In contrast to TMS protocols, the lack of lasting scalp sensations made patients totally unaware of the tDCS condition (anodal/cathodal/sham). To warrant a double-blind design, different researchers supervised the application of tDCS and of the experimental tasks.

Table 1 Demographic data of patients with progressive supranuclear palsy (PSP) and healthy controls (mean ± SD)

	Patients with PSP	Healthy controls
No. of participants	12	15
F/M	6/6	8/7
Age, y, mean ± SD	68.58 ± 6.35	64.13 ± 7.49
Handedness, R/L	12/0	15/0
Years of education, mean ± SD	14.25 ± 3.22	14.93 ± 2.69
Symptom duration, y, mean ± SD	4.33 ± 2.19	—

Brain stimulation

tDCS procedures were the same as previously described by Teichmann et al.[23] An MRI-guided stereotaxic frameless neuronavigation system (Brainsight, Rogue Research, Canada) guided tDCS electrode placement to ensure the shortest straight path to the cortical target. Stimulation targets for anodal and cathodal tDCS of the left and right DLPFC corresponded to the Montreal Neurological Institute (MNI) coordinates (x = −36, y = 32, z = 47) and (x = 39, y = 32, z = 45),[20] respectively, whereas a contralateral supraorbital electrode (right and left supraorbital region, respectively) was used as return. The scalp location of active tDCS electrodes corresponded to ~F3 (left-anodal) and ~F4 (right-cathodal) according to the 10–20 EEG reference system, and the contralateral supraorbital return electrodes were placed on ~AF8 and AF7, respectively. Active stimulation was delivered with round sponge electrodes (5.65 cm diameter, 25 cm^2 surface, Neuroelectrics SPONSTIM 25) at an intensity of 1.59 mA (current density 0.06 mA/cm^2). The current was kept at this intensity during 20 minutes before being ramped down along 30 seconds. During sham stimulation, the current was ramped up and down during 30 seconds at the initial and final phase of the session to emulate the transient skin itching sensations characterizing active stimulation.

To ensure safety and assess tolerance to stimulation, patients completed a tDCS adverse effects questionnaire[29] that rates side effects within a set of the most frequent effects reported in tDCS studies (e.g., itching, tingling, skin redness).

Computer simulations of current density distribution

A finite element method model was developed on a detailed standardized head volume (ICBM-NY) to determine the peak electric field, current density, and their distribution on the cortical surface. A mean anatomical MRI volume using data from 152 individuals (ICBM152/MNI152) was segmented into 6 conductive volumes: air, skin, skull, CSF, gray matter, and white matter for modeling. Lingering errors in continuity and detail were corrected manually within the image volumes at a resolution of 0.5 mm^3. MNI targets of the right and left DLPFC areas were coregistered to the ICBM-NY model in SPM8 to recreate the tDCS experimental conditions of the study.

Two tDCS conditions were modeled with scalp electrodes targeting the aforementioned MNI coordinates (shortest straight path to target): anodal and cathodal tDCS over the

left and right DLPFC, respectively. Stimulation electrodes and sponge pads (5.65 cm diameter, 25 cm^2 surface) were modeled in SolidWorks (Dassault Systems Corp., Waltham, MA) and imported into ScanIP for meshing. An adaptive tetrahedral meshing algorithm was used in ScanIP M-2017.06 (Simpleware, Exeter, UK) to generate meshes with approximately 10 million quadratic elements. Finite element method models were created in COMSOL multiphysics 5.1 (COMSOL, Inc., Burlington, MA) using electrostatic volume conductor physics with material conductivities defined as follows (in S/m): air, 1×10^{-15}; skin, 0.465; skull, 0.01; CSF, 1.65; gray matter, 0.276; white matter, 0.126; electrode, 5.99×10^7; saline-soaked sponge, 1.4. The former values were the same as previously published modeling work drawing on data from a combination of in vivo and in vitro measurements' employed in neurodegenerative patients.[23]

Internal boundary conditions between tissue layers were implemented to simulate direct current stimulation and assigned the continuity condition ($n^*[J1 - J2] = 0$), to solve the Laplace equation ($\nabla^*[\sigma\nabla V] = 0$). The surfaces of the cathodes were grounded ($V = 0$), while the surfaces of the anodes were assigned inward normal current densities calculated to produce 1.59 mA of stimulation. All other exterior surfaces were electrically insulated. The resulting cortical electric field was interpreted as a correlate for modulation. The radial electric field was calculated as the vector projection of the cortical electric field onto the cortical surface normal ($n \cdot E$).

General cognitive/language assessment

Assessment with standardized tests contributed to PSP diagnosis and to the constitution of a relatively homogenous cohort with patients having similar levels of cognitive impairment and disease duration. The general cognitive assessment included the MMSE,[26] the FAB,[27] Trail-Making Test A,[30] an evaluation of aphasia severity (Boston Diagnostic Aphasia Evaluation[31]), a picture naming test (D080[32]), and a verbal fluency test (phonemic and category fluency).[33] Healthy participants were tested with the MMSE and the FAB. Test scores are summarized in table 2.

Experimental tasks

Experimental language tasks were designed to tap semantic and lexical access, which contributes to language initiation/fluidity. They allowed, unlike standard aphasia tests, for the matching of the stimuli on linguistic variables between different intratask conditions and between version 1 and version 2 of the tasks (prestimulation or poststimulation).

The category judgment task was applied to assess access to semantic representations. Participants judged whether a given word item belonged to a "living" or a "nonliving" semantic category. The material included 2 versions (prestimulation and poststimulation) to avoid retest effects. Both versions contained 20 words representing living items and 20 words representing nonliving items. Words representing living and nonliving items, and words of both versions of the task, were matched for lexical frequency, number of letters, and number of phonemes (all Fs < 1).[34] Each stimulus was displayed in the center of a computer screen for 6 seconds. Participants were asked to press the left trackpad button for living items, and the right button for nonliving items, using respectively the index and the middle fingers of their dominant hand. The order of living and nonliving stimuli was randomized.

Table 2 General cognitive/language assessment, mean ± SD

	Patients with PSP	Healthy controls	Normative thresholds
MMSE	25.80 ± 3.0	29.33 ± 0.72	≥27
FAB	14.30 ± 2.50	17.67 ± 0.49	≥16
TMT-A	90.4 ± 20.7	—	<40
BDAE: aphasia severity scale	3.60 ± 0.89	—	>4
Category fluency (fruits/2 min)	14.33 ± 6.53	—	≥15
Phonemic fluency (P/2 min)	13.0 ± 1.41	—	≥15
DO80	74.30 ± 5.03	—	>75

Abbreviations: BDAE = Boston Diagnostic Aphasia Examination; DO80 = picture naming test; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; PSP = progressive supranuclear palsy; TMT-A = Trail-Making Test version A.

The letter fluency task was used to assess lexical access and language initiation/fluidity. Participants were asked to generate orally in 1 minute as many words as possible beginning with a given letter (C or P). To limit retest effects, patients performed this task prior to and following stimulation either with the letter C (version 1) or P (version 2). Words beginning with C or P are similar in terms of number of items and they have a similar cumulative lexical frequency in French (both Fs < 1).[33]

To control for potential biases linked to executive dysfunction, independently from language deficits, we also tested tDCS effects on a spatial sequence generation task assessing executive control/attention capacities. Participants were asked to generate in 1 minute the highest number of sequences made of 4 items (white dots) within a set of 15 items arranged in a triangular configuration. They were requested to sequentially select on a tactile screen each item with the index finger of their dominant hand, and avoid repeating the same sequence or using items appearing in blue (blue dots). Two versions of the test with different spatial arrangements of white and blue dots were used during prestimulation and poststimulation.

The 2 language tasks were programmed with E-Prime software (Psychology Software Tools, Pittsburgh, PA) and were presented on a laptop computer (HP EliteBook 8770w). The

stimuli for the spatial sequence generation task were presented on a touch-sensitive screen tablet (HP Envy 8 x2). The order of version 1 and version 2 of each test was counterbalanced, with half of the patients receiving version 1 before tDCS (version 2 following tDCS) and half of the patients receiving version 2 before tDCS (version 1 following tDCS). The order of the tests was blocked: (1) letter fluency task, (2) spatial sequence generation task, (3) category judgment task. The tasks were completed in ~15 minutes, a period covered by the offline effects of 20 minutes of tDCS.[28]

The primary research questions were to explore whether tDCS over the DLPFC improves performance of patients with PSP in (1) the category judgment task (semantic access) or (2) in the letter fluency task (lexical access), while assigning a level of evidence corresponding to a Class III trial.

Data availability statement

Anonymized data, statistical methods, and experimental material not entirely published within the article will be shared by request from any qualified investigator.

Results

Computational model of current density distribution

Computer simulations predicted that both active tDCS stimulation strategies (left-anodal, right-cathodal) differentially modulate activity in the lateral and rostral aspects of their respective DLPFC targets. Directional current flow also indicated opposite modulatory effects.[35] The model characterized left-anodal stimulation as driving enhancements of activity across the left DLPFC and adjacent areas (where current flow is radially inward) and relative decreases (where current flow is radially outward) for right-cathodal tDCS. Moreover, as intended, both tDCS configurations (anodal tDCS and cathodal tDCS over the left and right DLPFC, respectively) generated an interhemispheric imbalance of prefrontal activity, with higher levels in left than right DLPFC.

Further supporting the efficacy of our electrode montage, the magnitude of the peak electric field and current density at each of the 2 MNI locations reached intensities (left and right DLPFC targets: 0.65 V/m and 0.18 A/m^2) comparable to those generated in prior tDCS studies showing preclinical efficacy, including investigations with substantiated neurophysiologic support.[36] The polarity of stimulation (anodal vs cathodal) was dependent on the orientation of the electric field with the cortical surface, which led to mixed polarities between the electrodes. However, currents in the regions of peak stimulation underneath the anode and cathode were predominately in the expected orientation (inward for anodal, outward for cathodal). Finally, our modeling work showed that the area of influence of tDCS fields spread across a cortical area, which encompassed the MNI targets of the left and right DLPFC. Results are illustrated in figure 1.

Experimental tasks at baseline: Patients vs controls

Analyses of variance (ANOVAs) showed that patients with PSP performed more poorly than healthy controls in the 2 language tasks: category judgment (75.8% ± 16.1% correct, 95% confidence interval [CI] 69.6%–80.2% [patients]; 98.8% ± 1.2% correct, CI 97.5%–99.1% [controls]; $F_{1,25}$ = 30.673, $p < 0.001$, CI of difference 18.1%–28.8%) and letter fluency (6.5 ± 4.9 words, CI 4.6–7.6 [patients]; 21.2 ± 5.8 words, CI 19–23.4 [controls]; $F_{1,25}$ = 48.989, $p < 0.001$, CI of difference 12.4–17.7). In the category judgment task, reaction times were slower in patients than in controls (1,615 ms ± 448 ms, CI 1,512 ms–1,825 ms [patients], 938 ms ± 145 ms, CI 879 ms–999 ms [controls]; $F_{1,25}$ = 30.357, $p <$ 0.001, CI of difference −896 ms to −564 ms). Performance in the spatial sequence generation task was poorer in patients than in controls (7 ± 2.9 sequences, CI 6–8 [patients]; 17.9 ± 2.9 sequences, CI 17.5–19.8 [controls]; $F_{1,25}$ = 165.8, $p <$ 0.001, CI of difference 10.1–13.2). Results are illustrated in figure 2.

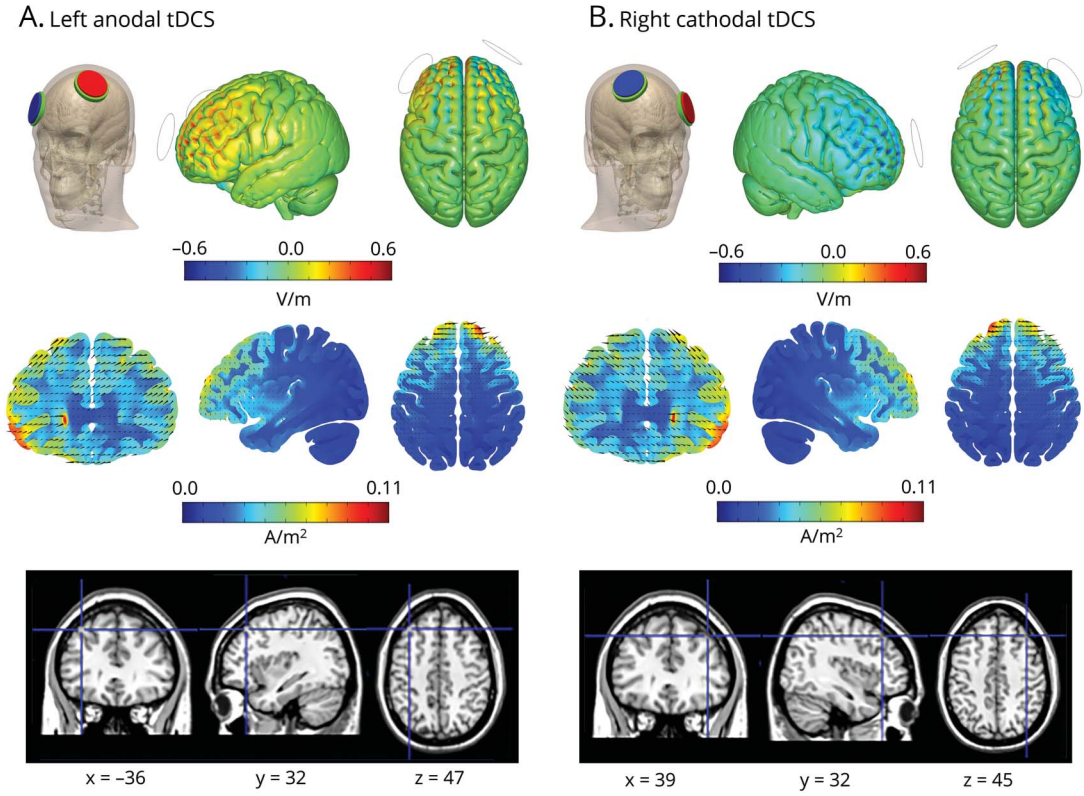
tDCS and language performance

ANOVAs contrasted prestimulation and poststimulation performance by comparing left-anodal and right-cathodal with sham stimulation. The independent variables were time point (prestimulation, poststimulation) and tDCS condition (left-anodal, right-cathodal, sham). Performance accuracy or reaction times were the dependent variables. Incorrect responses were excluded from the analyses of reaction times. Results are illustrated in figure 3 and table 3.

Results for the category judgment task showed a significant time point × tDCS condition interaction ($F_{2,22}$ = 5.850, p = 0.009). Restricted analyses demonstrated performance improvement following right-cathodal tDCS (81.7% ± 15.8% correct, CI 71%–91.5%), compared to prestimulation performance (71.7% ± 15.2% correct, CI 61.9%–81.1%; $F_{1,11}$ = 12.878, p = 0.004, CI of difference 3.4%–16.1%). In contrast, no effects between prestimulation vs poststimulation performance were found for sham stimulation (poststimulation 76.3% ± 18.8% correct, CI 63.9%–87.9%; prestimulation 75.2% ± 15.2% correct, CI 65.5%–84.8%; $F < 1$) or for left-anodal tDCS (poststimulation 76.2% ± 17.3% correct, CI 65.2%–87.1%; prestimulation 78% ± 17.7% correct, CI 66.8%–89.2%; $F < 1$). Results of the restricted analyses remained significant after correction for multiple comparisons using Bonferroni corrections. Baseline performance measured during the prestimulation test session was similar for the left-anodal, right-cathodal, and sham condition ($F_{2,33}$ = 0.497, p = 0.613). Left-anodal, right-cathodal, or sham tDCS did not show significant effects for reaction times (all Fs < 1).

Results for the letter fluency task showed no significant time point × tDCS condition interaction (F = 0.735, p = 0.467) but restricted analyses indicated improvement of poststimulation performance following left-anodal tDCS (7.3 ± 4.9 words, CI 4.2–10.5) compared to prestimulation performance (5.5 ± 4.5

Figure 1 Modeling of electric field and current density for anodal and cathodal transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC)



Predicted radial electric field and current density magnitude modeled for round 25 cm^2 sponge electrodes with a contralateral supraorbital reference on a standard head (ICBM-NY) for the 2 active electrode montages. (A) Left-anodal DLPFC tDCS. (B) Right-cathodal DLPFC tDCS, both with a contralateral supraorbital reference. Each panel presents an accurate account of relative electrode position and size with regards to head and scalp features. (Top) Anatomical model of electrode relative size and positioning, and radial electric field (V/m) distribution on cortical surface (by convention, the color scale was normalized so that cathodal [outward] electric field was presented in blue hues and anodal [inward] electric field in red hues); (middle) current density magnitude (A/m^2) and flow direction (current density magnitude was plotted in 2D slices with uniformly distributed arrows sized proportionally to the local current density magnitude); (bottom) coregistered coronal and sagittal MRI centered on Montreal Neurological Institute target coordinates (x = −36, y = 32, z = 47) and (x = 39, y = 32, z = 45) for left and right prefrontal targets, respectively. Note that whereas right-cathodal tDCS induced peak outward electrical field in the right prefrontal lobe, left-anodal tDCS induced opposite effects in a similar location of the left prefrontal lobe. The regions in which the effects of anodal or cathodal tDCS were modeled encompassed the coordinates of the intended cortical targets and colocalized tightly with them.

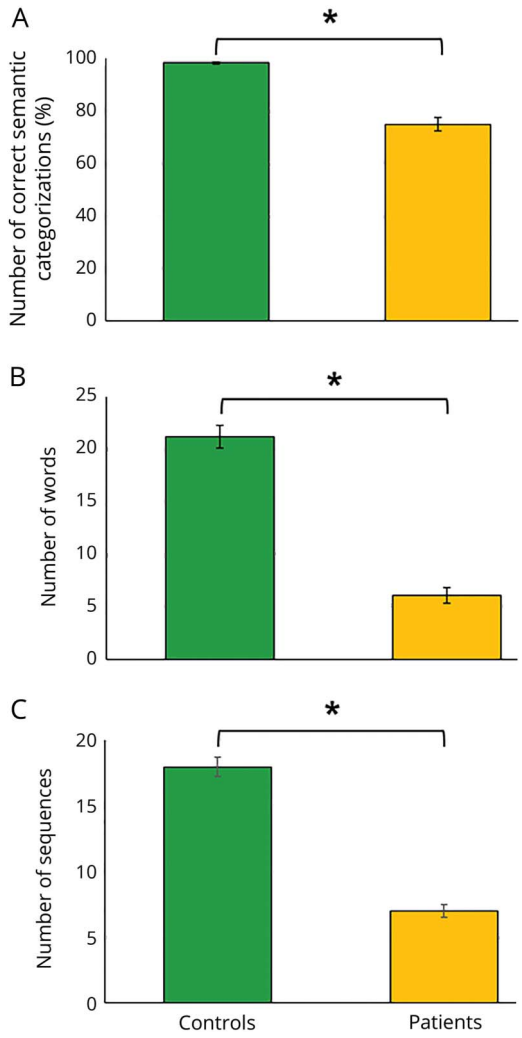
words, CI 2.6–8.4; $F_{1,11} = 6.969$, $p = 0.023$, CI of difference 0.3–3.4). In contrast, right-cathodal tDCS (prestimulation 6 ± 4.5 words, CI 3.1–8.9; poststimulation 7.1 ± 4.4 words, CI 4.4–9.9) and sham stimulation (prestimulation 6.8 ± 4.7 words, CI 3.8–9.8; poststimulation 7.5 ± 5.7 words, CI 3.8–11.2) did not modify performances (both Fs < 1). Results of the restricted analyses remained significant after correction for multiple comparisons using Bonferroni corrections. Baseline performance measured during the prestimulation test session was similar for the left-anodal, right-cathodal, and sham condition ($F_{2,33} = 0.259$, $p = 0.773$).

For the executive control task (spatial sequence generation) there was no time point × tDCS condition interaction ($F < 1$). Moreover, restricted analyses showed no differences between poststimulation and prestimulation performance for left-anodal (prestimulation 6.9 ± 3.5 sequences, CI 4.7–9.1; poststimulation 7.3 ± 4.9 sequences, CI 4.1–10.4), right-cathodal (prestimulation 6.6 ± 2.7 sequences, CI 4.9–8.3; poststimulation 7.3 ± 2.8 sequences, CI 5.3–9.2), and sham stimulation (prestimulation 7.5 ± 2.8 sequences, CI 5.7–9.3; poststimulation 7 ± 3.4 sequences, CI 4.8–9.2) (all Fs < 1).

To further strengthen these results, we checked for unlikely carryover effects of the 3 one-week-distanced tDCS sessions[28] by comparing the 3 prestimulation baselines for the 2 efficient tDCS modalities (left-anodal for letter fluency, right-cathodal for category judgment). Friedman tests showed that there were no differences among the 3 prestimulation performances (category judgment $\chi^2[2] = 2.79$, $p = 0.25$; letter fluency $\chi^2[2] = 4.33$, $p = 0.12$), demonstrating the absence of carryover biases.

We also checked that depression levels have not influenced the stimulation outcomes by performing Pearson correlations between depression scores (MADRS) and stimulation-driven performance improvements in the category judgment and the letter fluency task. There was no significant correlation between depression scores and performance improvements of category judgment ($r = −0.297$, $p = 0.35$) and letter fluency ($r = 0.018$, $p = 0.96$).

Figure 2 Performance of patients with progressive supranuclear palsy and healthy controls in the experimental tasks (mean values and standard error bars)



(A) Category judgment task. (B) Letter fluency task. (C) Spatial sequence generation task.

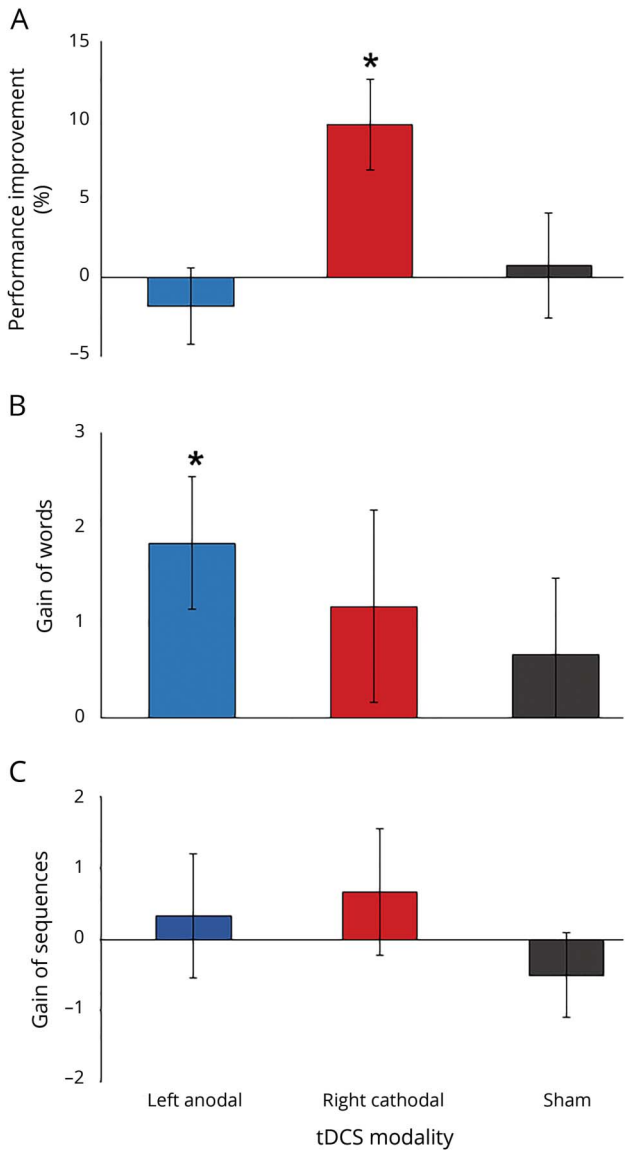
No side effects or any discomfort, as assessed by the tDCS adverse effects questionnaire,[29] were reported by any patient during or after the stimulation sessions.

Discussion

We explored the ability of tDCS to modulate language impairments in a cohort of patients with PSP using a double-blind sham-controlled crossover design. According to the principle of interhemispheric inhibition, we tested 2 stimulation strategies: anodal tDCS over the left DLPFC to directly boost the activity of language-related prefrontal regions, and cathodal tDCS over the right DLPFC to suppress inhibitory interhemispheric influences exerted by right prefrontal over left prefrontal systems. Our results show improvement of semantic access following right-cathodal tDCS as measured by the category judgment task. They also indicate that left-anodal tDCS improves lexical access and language initiation/fluidity as measured by the letter fluency task. In contrast, tDCS had no influence on executive capacities as assessed by the spatial sequence generation task. Furthermore, modeling of current distribution demonstrated that both anodal and cathodal tDCS reached sufficient peak current on the intended targets to influence adjacent prefrontal regions within the targeted hemisphere. Both tDCS strategies increased interhemispheric differences of prefrontal activity while boosting the left DLPFC. Our findings provide evidence for language improvements in patients with PSP via noninvasive neurostimulation and set the stage for therapeutic uses of tDCS with multiday regimens aiming at longer-lasting language effects by promoting neuroplasticity. Our results also enrich current knowledge about the role of the left DLPFC in language processing, and especially of lexical and semantic access mechanisms.

The issue whether transcranial stimulation can modulate language-related brain networks in neurologic diseases remains largely unsolved given contradicting results and methodologic shortcomings of most of the previous studies on poststroke or degenerative aphasia. The majority of these studies did not use double-blind or sham-controlled designs, and the different stimulation modalities such as anodal and cathodal tDCS, or high- and low-frequency TMS, were not counterbalanced in crossover designs. In addition, TMS studies using sham-controlled designs could not apply an effective sham condition given the hard-to-cancel sensory side effects, allowing patients to easily distinguish active from sham TMS.[37] The present study using a double-blind, sham-controlled, and counterbalanced crossover design aimed at clarifying whether tDCS can modulate language processing and its underlying networks to generate a rationale for its therapeutic application. Our findings demonstrated statistically significant effects on language processing by modulating prefrontal brain networks, as shown by our behavioral results with the support of modeling data on tDCS current distribution. They also strengthen prior findings by authors who highlighted the need for a rigorous methodology in pretherapeutic transcranial stimulation studies, which is indispensable for demonstrating statistically significant tDCS-induced language effects.[23] Our data furthermore indicate that stimulation effects are linked to the modulation of language-related processes rather than to nonspecific factors such as effects on general executive functioning. The probable language specificity in our study is suggested by the absence of tDCS effects on the non-language-related executive control task (spatial sequence generation). One should however note that tDCS generates effects on relatively large cortical regions, which could have modulated the activity of language-unrelated executive components of the left prefrontal cortex. Such putative modulations, not captured by the spatial sequence generation task, encourage future investigations using various executive tasks to explore whether tDCS-driven

Figure 3 Gain of function in the experimental tasks for the poststimulation/prestimulation contrast, comparing left-anodal and right-cathodal to sham transcranial direct current stimulation (tDCS) (mean values and standard error bars)



(A) Category judgment task. (B) Letter fluency task. (C) Spatial sequence generation task. Statistically significant gain of function for performance (poststimulation – prestimulation) is observed for the category judgment task after right-cathodal tDCS and the letter fluency task following left-anodal tDCS. Neither left-anodal nor right-cathodal tDCS had statistically significant effects on performances in the spatial sequence generation task testing executive control processes.

Table 3 Mean ± SD absolute values for prestimulation and poststimulation performances, for each task and stimulation modality

	Category judgment (total of 40 items)	Letter fluency (number of words)	Spatial sequence generation (number of sequences)
Prestimulation anodal	31.3 ± 6.8	5.5 ± 4.5	6.9 ± 3.5
Poststimulation anodal	30.6 ± 6.6	7.3 ± 4.9	7.3 ± 4.9
Prestimulation cathodal	28.7 ± 5.8	6.0 ± 4.5	6.6 ± 2.7
Poststimulation cathodal	32.6 ± 6.2	7.1 ± 4.4	7.3 ± 2.8
Prestimulation sham	30.2 ± 5.8	6.8 ± 4.8	7.5 ± 2.8
Poststimulation sham	30.5 ± 7.2	7.5 ± 5.8	7.0 ± 3.4

boosting of the left DLPFC might also improve some non-language-related executive capacities.

How does tDCS modulate the activity of cortices and brain networks underpinning language/semantic processing? In the present investigation, stimulation may have exerted a direct effect on language-related regions of the left prefrontal lobe following left-anodal tDCS, whereas similar effects were also indirectly achieved following right-cathodal tDCS via the suppression of interhemispheric inhibitory interactions between right/left DLPFC systems. This explanation finds support in our modeling study of current distribution in prefrontal regions revealing opposite local effects for anodal and cathodal tDCS on the left and right DLPFC, respectively. The left DLPFC, which was boosted in activity by both active stimulation strategies, has been shown to contribute to several language-related processes such as language activation/initiation and access to the mental lexicon and the semantic system.[38,39] However, this left prefrontal region does not host per se lexical or semantic representations. Nonetheless, it might contribute to the activation of search/retrieval processes for representations implemented in interconnected distant cortical areas of the left hemisphere such as the anterior temporal cortex for semantic information[40] or the temporal–parietal region for lexical representations.[41] Thus, in addition to direct effects on prefrontal regions, tDCS probably also modulates the activity of remote language areas via structural connectivity linking the stimulated left prefrontal cortices and the left temporal–parietal junction via the left arcuate fasciculus,[42] and anterior temporal cortices via the uncinate fasciculus.[42] This explanation is also coherent with recent fMRI studies indicating that anodal tDCS increases brain excitability in the targeted cortical area and modulates its functional connectivity with distant brain regions.[43] More specifically, an fMRI investigation has shown that anodal tDCS over the left DLPFC during a verbal fluency task increased functional connectivity between frontal and inferior parietal regions, which are part of the lexicon-related temporal–parietal junction.[44] Likewise, improvement of letter fluency in Parkinson disease after left-anodal DLPFC tDCS[45] suggests activity modulation of the left striatum contributing to lexical processing.[46] However, additional studies are needed to investigate the modulation of functional connectivity and the effects of tDCS on remote cortical regions.

Our study also allows for a comparison of effects between right-cathodal vs left-anodal tDCS. Regarding right-cathodal tDCS, the notion that local activity can be manipulated by suppressing transcallosal inputs from the opposite hemisphere relies on mutually inhibitory interhemispheric projections.[16] The modulation of interhemispheric interactions by noninvasive neurostimulation has been exploited in healthy participants and brain-damaged patients targeting right and left prefrontal, parietal, and temporal systems related to visuospatial attention,[47] verbal/spatial working memory,[48] or language/semantic performance.[15,21,23] Our results confirm that both tDCS strategies generate statistically significant language effects, yet in different domains. Semantic access (category judgment) was improved after right-cathodal tDCS whereas lexical access and language initiation/fluidity (letter fluency) was sensitive to left-anodal stimulation. These findings substantiate the validity of both left-anodal and right-cathodal tDCS approaches regarding language performance. However, they cannot provide an explanation regarding the differential effects of distinct stimulation strategies on distinct language processes.

Our findings also shed light on the role of prefrontal language systems. The results of the category judgment task revealing disorders of semantic access are consistent with investigations showing semantic difficulties in PSP.[6,9–12] In addition, our tDCS data demonstrate that semantic dysfunction can be improved by modulating left DLPFC activity. This finding is coherent with studies in healthy adults showing that the left DLPFC is activated in fMRI paradigms using semantic tasks.[49] Furthermore, probable tDCS effects on the connectivity with remote semantic-related areas is consistent with the fact that white matter tracts critical for semantic processes such as the uncinate fasciculus are damaged in PSP.[50] The results of the letter fluency task showing impaired performance in patients confirm that patients with PSP have verbal fluency deficits and deficient lexical access mechanisms.[9,10] Thus, in accordance with anatomo-functional correlation studies in PSP,[1,5] our data strengthen the view that the left DLPFC is a key region for the activation of language processes. More specifically, our findings suggest that the left DLPFC is part of a system controlling search mechanisms in the lexicon and in the semantic system, which are implemented by remote brain regions including the temporal–parietal junction and anterior temporal cortices.

tDCS delivered over the DLPFC efficiently seems to generate transitory modulations of left hemispheric language networks dedicated to several aspects of linguistic/semantic processing in patients with prefrontal lesions. This suggests pretherapeutic evidence for the improvement of language initiation and lexical and semantic access in PSP. The proof-of-concept provided by our study has implications for future uses of noninvasive neurostimulation as a therapeutic strategy in neurodegenerative language disorders. To achieve this goal, and to strengthen our findings, double-blind and sham-controlled trials with multiday tDCS regimens engaging enduring plasticity phenomena will be necessary to confirm therapeutically meaningful long-lasting effects in large PSP cohorts, or in other prefrontal pathologies affecting language processing.

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Disclosure

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Continued

Appendix (continued)

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