Direct Current Stimulation Over the Anterior Temporal Areas Boosts Semantic Processing in Primary Progressive Aphasia

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Objective: Noninvasive brain stimulation in primary progressive aphasia (PPA) is a promising approach. Yet, applied to single cases or insufficiently controlled small-cohort studies, it has not clarified its therapeutic value. We here address the effectiveness of transcranial direct current stimulation (tDCS) on the semantic PPA variant (sv-PPA), applying a rigorous study design to a large, homogeneous sv-PPA cohort.
Methods: Using a double-blind, sham-controlled counterbalanced cross-over design, we applied three tDCS conditions targeting the temporal poles of 12 sv-PPA patients. Efficiency was assessed by a semantic matching task orthogonally manipulating "living"/"nonliving" categories and verbal/visual modalities. Conforming to predominantly left-lateralized damage in sv-PPA and accounts of interhemispheric inhibition, we applied left hemisphere anodal-excitatory and right hemisphere cathodal-inhibitory tDCS, compared to sham stimulation.
Results: Prestimulation data, compared to 15 healthy controls, showed that patients had semantic disorders predominating with living categories in the verbal modality. Stimulation selectively impacted these most impaired domains: Left-excitatory and right-inhibitory tDCS improved semantic accuracy in verbal modality, and right-inhibitory tDCS improved processing speed with living categories and accuracy and processing speed in the combined verbal $\times$ living condition.
Interpretation: Our findings demonstrate the efficiency of tDCS in sv-PPA by generating highly specific intrasemantic effects. They provide "proof of concept" for future applications of tDCS in therapeutic multiday regimes, potentially driving sustained improvement of semantic processing. Our data also support the hotly debated existence of a left temporal-pole network for verbal semantics selectively modulated through both left-excitatory and right-inhibitory brain stimulation.

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Primary progressive aphasia (PPA) is a neurodegenerative disorder dramatically impairing language and communication abilities. It is subdivided into three main variants, including semantic PPA (sv-PPA), which represents the most frequent phenotype,[1] causing damage to the processing of word meaning and to predominantly left-sided cortices of the temporal poles.[2,3] Various studies have identified the linguistic-cognitive, anatomical, and biological features of sv-PPA,[4–7] but evidence-based therapy slowing language decline in PPA is lacking: Pharmacological trials with anti-Alzheimer's drugs have failed to provide significant results,[8] speech therapy has evidenced only small effects without generalization to untrained items,[9] and noninvasive brain stimulation investigations, which represent a promising approach, have not used controlled, double-blind designs and have never been applied to cohorts of sv-PPA.[10–15]

Noninvasive stimulation technologies, including transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS), have generated encouraging results, especially in poststroke aphasia when targeting language-related cortices, such as Broca's or Wernicke's area.[16–20] Most researchers used excitatory stimulation of the left-hemisphere language network to promote remapping of function and/or inhibitory stimulation to homotopic right-sided cortices, assuming that homotopic areas decrease activity in left-lateralized language areas through interhemispheric inhibitory projections.[21,22] However, these investigations were subjected to biases given the high variability of vascular lesion localization and extent. Such biases appeared to be circumvented in three small-cohort studies using stimulation in more-homogenous PPA populations while generating promising results.[13–15] However, these studies suffered from substantial limitations: They could not apply rigorously controlled and counterbalanced study designs, did not explore the most frequent PPA variant (sv-PPA), and they primarily targeted the nonlanguage specific dorsolateral prefrontal cortex.

The present tDCS study therefore explored a relatively large cohort of clinically and imaging-characterized sv-PPA patients, used a double-blind, sham-controlled, and counterbalanced cross-over design, targeted specifically temporal poles implementing semantics, and applied multidimensional semantic markers to evaluate stimulation efficiency. Following a rationale of interhemispheric inhibition through transcallosal connections between the temporal poles,[23] and accounting for predominant left temporal pole damage in sv-PPA,[2] we assessed both the impact of single left-excitatory and right-inhibitory tDCS sessions, as compared to sham stimulation. To evaluate whether potential stimulation-induced effects are genuinely linked to semantic modulation, we assessed two semantic categories ("living" vs "nonliving") and processing modalities (verbal vs visual), predicting selective modulations within the semantic system itself. According to findings that verbal, but not visual, semantics is related to the left temporal pole,[24] that sv-PPA primarily affects the verbal modality and living category,[7,25] and that stimulation effects prevail in the most damaged domains,[13] we predicted semantic-specific effects mainly in verbal/living aspects.

In addition, we expected to contribute to the controversy opposing models of amodal semantics equally involving both temporal poles[26,27] and multisystem accounts positing a particular system for verbal semantics in the left temporal pole.[24] Our experimental approach specifically challenged the latter view by testing semantic operations in the verbal versus visual modality while assessing potential semantic modulation through stimulation-induced boosting of the left temporal pole.

Patients and Methods

Participants

Twelve patients with sv-PPA were enrolled in the study at the National Reference Center for "PPA and Rare Dementias" of the Pitié-Salpêtrière Hospital (Paris, France). Clinical diagnosis was based on a multidisciplinary evaluation, including neurological examination, neuropsychological tests, and a detailed language evaluation. Definite diagnosis of sv-PPA was based on the current research criteria[3] comprehending progressive language impairment, single-word comprehension deficits, and anomia, without sentence repetition impairment, agrammatism, or motor speech disorders. All the patients also fulfilled the imaging-supported criteria for sv-PPA (ie, predominant hypometabolism of the anterior temporal region).[3] No patient had medication interfering with the central nervous system, with the exception of one patient who had taken, during 4 years, an antidepressant agent (citalopram, 20mg/day). The dosage of this medication had not been modified during the 3 years preceding his participation in the current study. We also included 15 healthy controls to determine normal performance levels with the semantic task and to provide a detailed characterization of semantic deficits in the patient group. Healthy controls were matched with the patients for handedness, gender, age, and years of education (all Fs < 1). Patients were not included if they had: (1) psychiatric disorders or neurological diseases other than sv-PPA; (2) contraindication for magnetic resonance imaging (MRI) or tDCS, such as intracranial ferromagnetic devices, scalp or skull lesions, or epilepsy; (3) MRI revealing pathological processes other than those associated with sv-PPA, including white matter vascular damage; (4) important severity of aphasia (severity score <2 of the Boston Diagnostic Aphasia Evaluation [BDEA][28]), Mini–Mental State Examination (MMSE) scores <15,[29] Frontal Assessment Battery (FAB) scores <10,[30] or major depressive disorders. All participants were native French speakers. Demographic data are summarized in Table 1. The study received approval from the French National Ethics Committee, and written informed consent was obtained from all the patients and healthy controls.

TABLE 1. Demographic Data of the sv-PPA Patients and Healthy Controls (Mean Scores ± Standard Deviations)

Tests	sv-PPA	Healthy Controls
No. of patients	12	15
Women/men	4/8	5/10
Age (yr)	66.8 ± 2.1	64.1 ± 7.4
Years of education	13.2 ± 1	14.9 ± 2.7
Handiness (R/L)	12R/0L	15R/0L
Symptom duration (yr)	5.3 ± 0.8	—
Age at disease onset	60.7 ± 8.1	—

sv-PPA = semantic variant of primary progressive aphasia; R = right; L = left.

Study Design

We applied a double-blind, sham-controlled, cross-over design in which each patient underwent three tDCS sessions: anodal tDCS (left temporal pole); cathodal tDCS (right temporal pole); and sham tDCS (left temporal pole). tDCS was used, rather than TMS, because of its wider range of cortical action, which appears to be of advantage in degenerative conditions. Stimulation was preceded and immediately followed by a semantic task providing markers for potential stimulation efficiency. The order of the three stimulation sessions was counterbalanced across the 12 patients to avoid order biases (6 permutations × 2), and the sessions were separated 1 week to prevent unlikely carry-over effects of the stimulation. The three tDCS sessions were scheduled at similar time slots during the day. To ensure a double-blind procedure, the semantic task and stimulation were supervised by two distinct researchers, and patients were completely unaware of whether real or sham conditions were applied.

Brain Stimulation

All patients underwent MRI to identify temporal pole coordinates. Scans were obtained less than 1 month before the stimulation sessions using a 3-Tesla scanner (VERIO system; Siemens, Erlangen, Germany) with a 32-channel head coil, including anatomical three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo images (repetition time = 2.3 seconds; echo time = 4.18ms; flip angle = 9 degrees; inversion time = 900ms; voxel size = 1 × 1 × 1mm^3; 176 slices). Images were registered in Montreal Neurological Institute (MNI) space, and the left and right temporal poles were identified and labeled by means of a 5-mm sphere on the coordinates [x = −52, y = 2, z = −28] and [x = 53, y = 4, z = −32],[31] using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were then denormalized in each patient's native space, and a frameless stereotaxic neuronavigation software (Brainsight, Rogue System; Rogue Research Inc., Montreal, Quebec, Canada) was used to identify the target regions and guide the placement of the active tDCS electrodes. Correct and consistent electrode placement was achieved by aligning the center of the electrodes with the orthogonal projection of the MNI-defined targets toward the closest skin area overlaying the temporal bone. This procedure ensured, for each patient, the shortest path length between the electrode surface and the target location in the cortical surface of the temporal poles. The scalp location of the active tDCS electrodes corresponded to FT8 to FT10 (right temporal) and FT7 to FT9 (left temporal) sites of the 10-20 EEG (electroencephalography) reference system. The reference electrode was placed on a contralateral supraorbital region with regard to the active electrode location (AF7 for right temporal tDCS and AF8 for left temporal tDCS in the 10-20 EEG reference system).

Electrodes were placed under MRI guidance (round sponge pads, 5.65cm in diameter, 25-cm^2 surface; [NE026a] SPONSTIM 25; Neuroelectrics, Barcelona, Spain) and were kept on their locations by a lycra EEG/tDCS cap attached to the chin (Neuroelectrics). Before electrode placement, hair was set apart and skin cleaned with alcohol and light abrasive gel to optimize electrode-to-skin conductance. Electrode leads were connected to a portable wireless stimulation unit (Neuroelectrics), attached to the dorsal portion of the cap, which was linked wirelessly by *bluetooth* connection to a laptop computer running data acquisition software (NIC software; Neuroelectrics). Each relevant tDCS stimulation parameter, such as stimulation modality (anodal, cathodal, and sham), duration, current intensity, and electrode montage, was programmed before the session and their settings were transferred by *bluetooth* to the stimulation unit.

During anodal or cathodal tDCS, current intensity was linearly increased during 30 seconds to reach a maximum of 1.59mA. This specific level of tDCS intensity was chosen to ensure, with our slightly smaller round electrodes (25cm^2), similar levels of current density (0.06mA/cm^2) as those applied in poststroke aphasia or PPA.[15,32] The current was kept on at this intensity during 20 minutes before being ramped down along 30 seconds. During sham stimulation, electrodes were placed in the same location as for anodal stimulation, but current was ramped up and down along 30 seconds at the initial and final phase of the session to emulate the transient skin-itching sensations characterizing active stimulation. Unnoticed by the patients, the stimulation unit was turned off during the 20 minutes of the sham session. At the end of each of the three stimulation sessions, we debriefed with every individual patient and asked them about their sensations during the stimulation. As expected, regardless of the tDCS condition (anodal, cathodal, or sham), they all reported a transient and mild local skin-itching sensation at the beginning of the stimulation, which dissipated quickly thereafter until disappearing. Importantly, none of the patients reported local scalp discomfort or showed signs of skin rash, reddishness, or inflammation, undesirable events that could have also provided patients with a clue for distinguishing active tDCS conditions from sham.

During the stimulation sessions, patients performed a simple visuomotor task consisting in pressing a response button every time a slowly moving round target touched the edge of a surrounding rectangle. This procedure ensured that patients did not close their eyes and maintained vigilance.

Computer Simulations of Current Density Distribution

A finite element method (FEM) model was developed on a detailed standardized head model (ICBM-NY) to determine the peak electric field, current density, and their distribution on the cortical surface. An averaged anatomical MRI volume consisting of 152 individuals (ICBM152/MNI152) was previously segmented into six conductive volumes: air, skin, skull, cerebral spinal fluid (CSF), gray matter, and white matter.[33] Lingering errors in continuity and detail were corrected manually within the image volumes at a resolution of $0.5mm^3$. The empirically derived MNI targets were coregistered to the ICBM-NY model in SPM8 to recreate experimental conditions.

Two experimental tDCS conditions were modeled: anodal tDCS on the left temporal pole and cathodal tDCS on the right temporal pole, according to the aforementioned MNI coordinates. Stimulation electrodes and sponge pads (5.65cm in diameter, 25-cm^2 surface; [NE026a] SPONSTIM 25; Neuroelectrics) were modeled in SolidWorks (Dassault Systèmes Corp., Waltham, MA) and imported into ScanIP for meshing. An adaptive tetrahedral meshing algorithm was used in ScanIP (version 7.0; Simpleware, Exeter, UK) to generate meshes with approximately 10 million quadratic elements. FEM models were created in COMSOL multiphysics (version 4.3; COMSOL, Inc., Burlington, MA) using the aforementioned meshes.

Models were created 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}; and saline-soaked sponge, 1.4. These conductivity values used were the same as in previously published work modeling work drawing on data from a combination of in vivo and in vitro measurements.[34–36] We applied boundary conditions to simulate direct current stimulation. Internal boundaries between tissues were assigned the continuity condition ($n * (J1 - J2) = 0$), and the Laplace equation ($\nabla * (\sigma \nabla V) = 0$) was solved. The resulting cortical electric field was interpreted as a correlate for modulation.[37,38] The surfaces of the cathodes were grounded ($V = 0$), whereas the surfaces of the anodes were assigned inward normal current densities calculated to produce 1.59mA of stimulation. All other exterior surfaces were electrically insulated. Radial electric field was calculated as the vector projection of cortical electric field onto the cortical surface normal ($n \cdot E$). By convention, the color scale was normalized so that cathodal (outward) electric field is blue and anodal (inward) electric field is red. Current density magnitude was plotted in two-dimensional slices with uniformly distributed arrows sized proportionally to the local current density magnitude. We further studied the impact on cortical electric fields current density levels of cortical loss (−0.5mm atrophy) affecting the two anterior thirds of the left and right temporal lobe of PPA patients. Level of atrophy was calculated as the mean levels of cortical loss in the left and right temporal lobe in an independent cohort of 12 sv-PPA patients, matched for disease duration and age with the 12 patients of the present study, and compared to 15 age-matched controls (left anterior temporal lobe: −21.05%, −0.61 mm; right anterior temporal lobe: −20.85%, −0.60 mm), and was adapted to the spatial resolution of our FEM head model.

Semantic Task

We used a computerized semantic matching task in a verbal and visual processing modality contrasting living and nonliving items to identify the specific deficit pattern in sv-PPA and provide markers of potential stimulation efficiency. Similarly to the Pyramid and Palm Trees Test (PPT),[39] each experimental stimulus consisted in a test item (top of the computer screen), a semantically related target (bottom, left, or right), and an unrelated distractor (bottom right or left). In half of the stimuli, the target was located at the left bottom side of the screen (distractor on the right), and in the other half, the target was presented at the right bottom side (distractor on the left). Half of the stimuli consisted in living items and the other half in nonliving items. All stimuli were presented in a verbal (written words) and a visual format (pictures). Illustrative stimuli are shown in Figure 1. In total, the materials consisted of 104 stimuli (52 verbal, 52 visual, containing each 26 living and 26 nonliving items). Pictures for the visual format were selected from a database of black and white line drawings.[40]

The entire test material was split into two distinct, but matched, versions for assessing alternatively pre- and poststimulation performance, therefore avoiding retest effects. This procedure yielded four stimulus blocks, each containing 26 stimuli with 13 stimuli comprehending living and 13 nonliving items (version 1 verbal block, version 1 visual block; version 2 verbal block, version 2 visual block). Test items, targets, and distractors of the two versions were matched for lexical frequency, number of letters, concept familiarity, visual complexity, and picture naming consensus[41] (all Fs < 1). Within each version, targets and distractors of verbal stimuli with living and with nonliving items were matched for lexical frequency, number of letters, and concept familiarity (all Fs < 1). Likewise, within each version, targets and distractors of visual stimuli with living and with nonliving items were matched for concept familiarity, visual complexity, and picture naming consensus (all Fs < 1). The order of verbal and visual blocks was counterbalanced across the 12 patients, and stimulus order within a given block was randomized. Similarly, the order of version 1 and version 2 was counterbalanced, with half of the patients receiving version 1 before the stimulation (version 2 after stimulation) and half of the patients receiving version 2 before stimulation (version 1 after stimulation).

Stimuli were presented on a laptop computer (*HP EliteBook 8770w*; Hewlett Packard, Palo Alto, CA) with *E-Prime* software. Each trial consisted in the presentation of a fixation cross for 1,000ms in the middle of the computer screen, followed by the stimulus centered in the same position. Participants were placed approximately 30cm from the computer

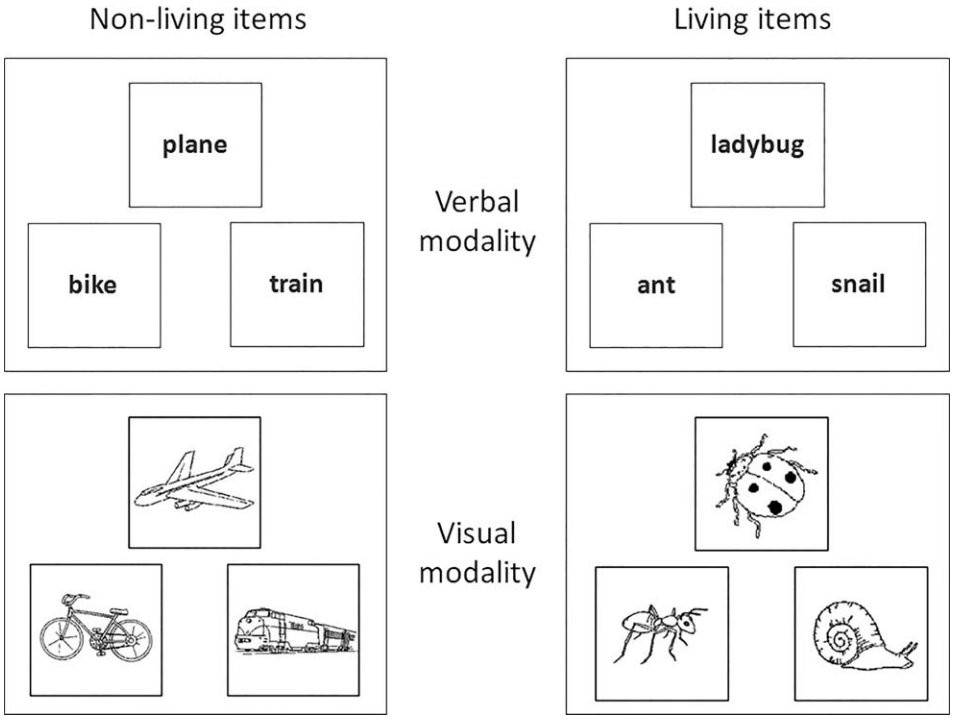

FIGURE 1: Illustrative items of the semantic matching task including verbal (written words) and visual (pictures) conditions, and living and nonliving conditions.

screen and were instructed to decide as accurately and as quickly as possible which of the two items at the bottom of the screen (target, distractor) was related to the test item (top of the screen). Answers were provided by pressing a right or left response button, with the index/middle finger of the dominant hand corresponding to the right or left location of the chosen item. Stimuli remained for 600ms on the computer screen before a new trial was initiated. The testing procedure required around 10 minutes to be completed. This duration is within the poststimulation period usually covered by offline effects after 20 minutes of tDCS.[42] The same materials and procedure were also used in healthy controls who did not receive tDCS.

General Language/Cognitive Assessment

The assessment with standardized tests contributed to the diagnosis of sv-PPA and allowed for constituting a relatively homogeneous patient population by identifying participants with similar levels of disease severity and duration. The language assessment was composed of an evaluation of aphasia severity (BDAE[28]), a picture naming test (D080[43]), a single-word comprehension task requiring pointing to pictures upon auditory word presentation (BDAE), a verbal fluency test comprising phonemic and category fluency,[44] a sentence repetition task (BDAE), and a semantic matching task in a visual and verbal version (PPT[39]). General cognitive assessment included the MMSE[29] and the FAB.[30]

Positron Emission Tomography Imaging

The positron emission tomography (PET) study allowed for checking that patients fulfilled the imaging-supported diagnosis criteria for sv-PPA. All patients underwent fludeoxyglucose-PET (^{18}FDG-PET) brain less than 1 month before the stimulation sessions. Images were acquired with a hybrid PET/CT (computed tomography) system (Gemini XLS; Philips Medical Systems B.V, Best, The Netherlands) 30 minutes after the intravenous injection of ^{18}FDG (2.5MBq/kg). During ^{18}FDG injection and until image acquisition, patients were asked to rest in a quiet environment with eyes closed. A CT scan was recorded to provide an attenuation-correction map and was followed by a 15-minute emission scan consisting of a single frame. PET images were reconstructed using iterative reconstruction and were corrected for gamma-ray attenuation and scatter.

Metabolic data were analyzed using SPM8 software (Welcome Department of Cognitive Neurology, University College, London, UK) implemented in MATLAB (The MathWorks, Inc., Natick, MA). PET images were spatially normalized into the MNI space, smoothed, and adjusted in global metabolism using the cerebellum as the reference region. Metabolism was compared between the 12 sv-PPA patients and 15 age-matched healthy adults, entering age also as a confounding variable. Considering the small sample size, SPM(T)maps were thresholded at $p < 0.05$ corrected for multiple tests using the family-wise error (FWE) method. Only clusters of more than 100 voxels were considered.

TABLE 2. Scores of sv-PPA Patients on the General Cognitive and Language Assessment

Tests	Means ± SD	Normal Threshold
MMSE	23.7 ± 0.9	≥29
FAB	13.5 ± 0.5	≥16
Aphasia severity rating scale (BDAE)	3.5 ± 0.7	>4
Naming (DO80)	28.2 ± 17.5	≥30
Single-word comprehension (BDAE)	54.3 ± 8.5	≥70
Pyramids and palm trees test verbal	33.0 ± 7.9	≥45
Pyramids and palm trees test visual	33.6 ± 9.5	≥45
Sentence repetition (BDAE)	14.1 ± 1.6	≥14
Category fluency ("fruits" per 2 minutes)	5.6 ± 3.1	≥15
Phonemic fluency ("P" per 2 minutes)	13.5 ± 4.5	≥15

sv-PPAS = semantic primary progressive aphasia variant; SD = standard deviation; MMSE = Mini–Mental State Examination; FAB = Frontal Assessment Battery; BDAE = Boston Diagnostic Aphasia Examination.

Results

General Language/Cognitive Assessment

Patients demonstrated abnormal scores on semantic-related tasks such as the DO80 naming test, the PPT, and single-word comprehension. By contrast, performance with non-semantic-related tests, such as, for example, sentence repetition, was normal. Besides confirming sv-PPA diagnosis, results also demonstrated small standard deviations on test scores, indicating considerable homogeneity of the patient cohort. Results are summarized in Table 2.

PET Imaging

Compared to healthy controls, and according to imaging-supported sv-PPA diagnosis criteria, patients had bilateral hypometabolism with a left predominance in the temporal poles, hippocampi, and the fusiform, and parahippocampal gyri ($p < 0.05$, FWE corrected; Fig 2; Table 3).

Computational Model of Current Density Distribution

Computer simulations predicted that both active tDCS conditions differentially modulate activity in the anterior and lateral aspects of the targeted temporal poles. Directional current flow indicates opposite modulatory effects,[45–49] in which left anodal stimulation is expected to enhance activity in the left temporal pole and adjacent areas (where current flow is radially inward), whereas right cathodal stimulation induces relative decreases (where current flow is radially outward; see Fig 3A,B). Further supporting the efficacy of our electrode montage, the magnitude of the peak electric and current density values at each of the two MNI target locations reached significant values in both locations (left temporal target: 0.27V/m and 0.075A/m^2; right temporal target: 0.28V/m and 0.077A/m^2), with intensity levels comparable to those generated in other tDCS studies, including substantiated neurophysiology.[50–53] Finally, our modeling work showed that the area of influence of the tDCS modulatory effects spread in relatively constrained region over the cortex, encompassing the MNI-defined left and right temporal pole targets ([x = −52, y = 2, z = −28] and [x = 53, y = 4, z = −32]), which were the targets aimed during the placement of the electrode pads as projections from the scalp. Importantly, these two sites colocalized with the most impacted hypometabolic regions revealed by PET in the anterior and lateral aspects of the temporal lobe of our patients (see details in Fig 3C). In comparison to previously published tDCS models of stimulation, primarily over the parietal or frontal bones, the high focality of this particular "1 × 1" montage could be explained by the convexity and relatively thinness of the temporal bone. Additional models implementing levels of regional cortical atrophy (thinning of ~0.5mm in sv-PPA vs age-matched controls) indicated a minor impact on current flow through the anterior temporal lobe and the intended MNI target sites (Fig 3D).

Semantic Task: Patients vs Healthy Controls

Analyses of variance (ANOVAs) were conducted with the patient data collected in the test sessions before brain stimulation and with data from the healthy controls. Group (patients, controls), modality (verbal, visual) and category (living, nonliving) were used as independent variables and performance as the dependent variable. In a second series of ANOVAs, reaction times were used as the dependent variable, with incorrect responses being excluded from the analyses.

Performance was lower in patients (57% ± 16 correct) than in controls (95% ± 6 correct; $F_{(1,25)} = 141.3$; $p < 0.001$). There was a modality effect ($F_{(1,25)} = 4.7$; $p = 0.04$), a category effect ($F_{(1,25)} = 20.2$; $p < 0.001$), a group × modality interaction ($F_{(1,25)} = 8.3$; $p = 0.008$), and group × category interaction ($F_{(1,25)} = 9.2$; $p = 0.006$). The interactions were linked to the fact that

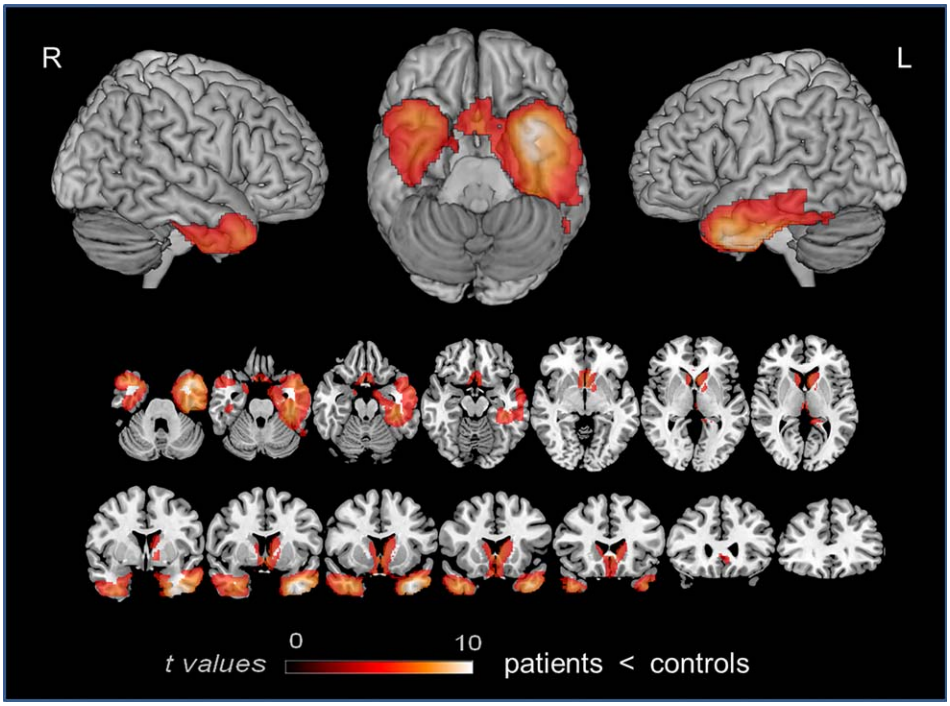

FIGURE 2: Cortical hypometabolism in sv-PPA as compared to healthy controls on FDG-PET. Cortical metabolism is severely decreased (hot colors) in the bilateral temporal poles with left predominance ($p < 0.05$ family-wise error corrected). FDG-PET = fludeoxyglucose positron emission tomography; L = left; R = right; sv-PPAS = semantic primary progressive aphasia variant.

patients had poorer performance in the verbal (51% ± 15 correct) than in the visual modality (63% ± 12 correct; $F_{(1,11)} = 7.4$; $p = 0.02$), whereas healthy controls had similar performance in both modalities (verbal: 96% ± 5 correct; visual 95% ± 6 correct; $F < 1$). Likewise, patients demonstrated poorer performance with the living category (54% ± 11 correct) than with the nonliving category (61% ± 13 correct; $F_{(1,11)} = 18.7$; $p = 0.001$), whereas healthy controls showed similar performances with both categories (living: 94% ± 5 correct; nonliving: 96% ± 3 correct; $F_{(1,14)} = 2.8$; $p = 0.12$). Results are illustrated in Figure 4.

Reaction times were slower in patients (3,375ms ± 809) than in healthy controls (2,012ms ± 399; $F_{(1,25)} = 51.7$; $p < 0.001$). There was a modality effect ($F_{(1,25)} = 12.3$; $p = 0.002$) and a group × modality

TABLE 3. Voxel-Based Comparison Between sv-PPA and Healthy Controls on Brain Metabolism

Cluster Size (no. of voxels)	p corr.	T	Z Score	Coordinates (mm)			Brain Region (Brodmann Area [BA])
				x	y	z	
Healthy controls minus sv-PPA patients							
8,410	**<0.001**	**11.7**	**6.7**	**−34**	**8**	**−32**	**Left temporal pole (BA 38)**
		11.4	6.6	−38	−10	−35	Left inferior temporal gyrus (BA 20)
		9.0	5.9	−40	−26	−21	Left inferior temporal gyrus (BA 20)
3,170	**<0.001**	**9.0**	**5.9**	**32**	**12**	**−31**	**Right temporal pole (BA 38)**
		8.1	5.6	38	−8	−33	Right fusiform gyrus (BA 20)

Coordinates are in millimetres relative to the anterior commissure, corresponding to the MNI space. Statistical maps were thresholded for significance at $p < 0.05$ FWE-corrected for the comparisons between controls and sv-PPA. Cluster extent was set at 100 voxels.
sv-PPAS = semantic primary progressive aphasia variant; FWE = family-wise error; MNI = Montreal Neurological Institute.
Bolded rows and values can be substituted by unbolded/normal characters.

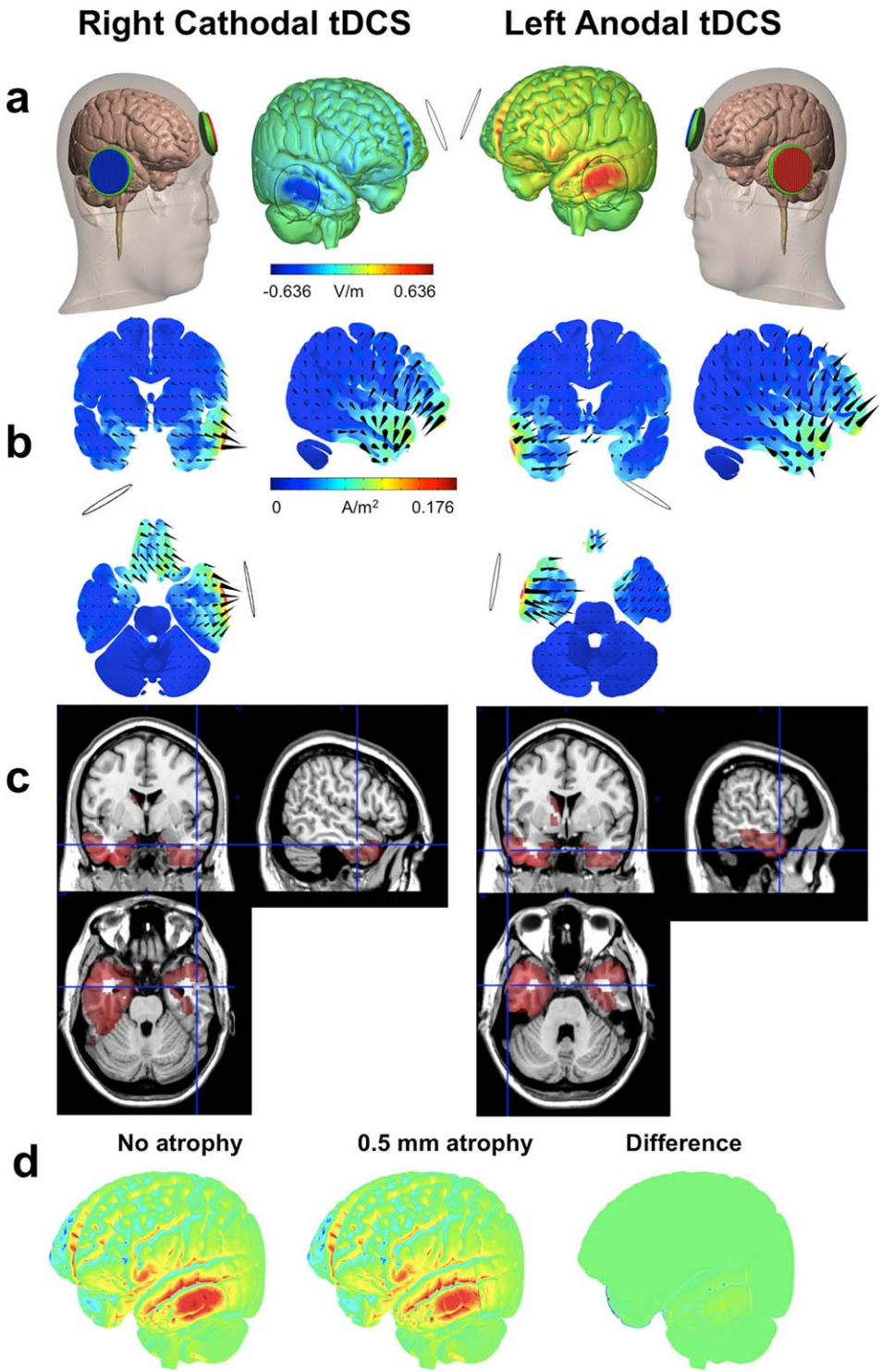

FIGURE 3: Predicted radial electric field (A) and current density magnitude (B) in comparison to empirically derived hypometabolic regions of interest (C). Round 25-cm^2 electrodes with a contralateral supraorbital reference were modeled on a standard head (ICBM-NY) for the two active electrode montages used in the current study: right temporal pole, cathodal-inhibitory tDCS (right column) and left temporal pole, and anodal-excitatory tDCS (left column) with a contralateral supraorbital reference. The figure presents a highly accurate account of relative electrode position and size with regard to head features: (A) anatomical model of electrode relative size and positioning and radial electric field (V/m) distribution on cortical surface; (B) current density magnitude (A/m^2) and flow direction; and (C) areas of hypometabolism coregistered with coronal, sagittal and sagittal magnetic resonance imaging images centered on MNI target locations ([x = −52, y = 2, z = −28] and [x = 53, y = 4, z = −32]. Notice that whereas cathodal tDCS induced peak outward electric field in the lateral and rostral right temporal lobe, left anodal tDCS induced opposite effects in a similar location of the left temporal lobe. The regions in which the impact of anodal or cathodal tDCS was modeled encompassed the coordinates of the intended cortical targets and colocalized tightly with them. (D) Impact of left anterior temporal lobe atrophy (−0.5-mm loss) on radial electric field (V/m) distribution across the cortical surface generated with tDCS currents (same color scale as in [A]). Note that the difference in the impact of tDCS current over the anterior two thirds of an atrophic versus a nonatrophic temporal lobe is very weak. The effect of atrophy on left anodal and right cathodal stimulation is nominally symmetric; hence, only the model for the former is shown. MNI = Montreal Neurological Institue; tDCS = transcranial direct current stimulation.

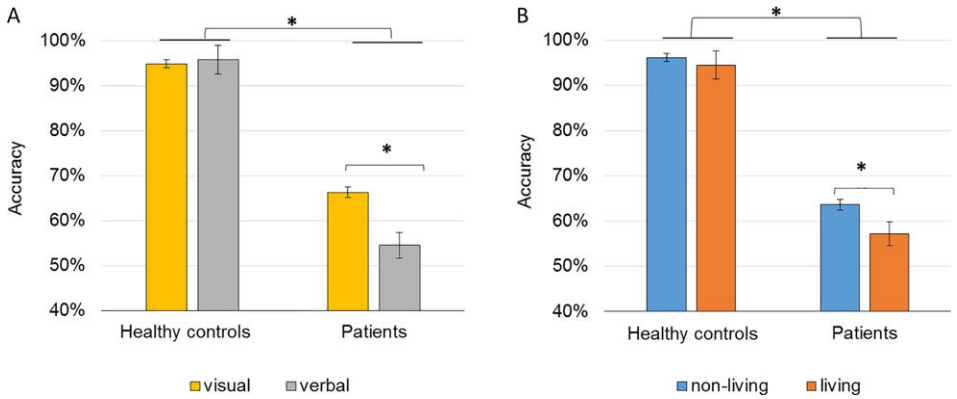

FIGURE 4: Performance of sv-PPA patients and healthy controls (mean values and standard errors) with verbal versus visual show (panel A) and living versus nonliving (panel B) items, showing a predominant impairment in patients for the verbal modality and the living category. sv-PPAS = semantic primary progressive aphasia variant.

interaction ($F_{(1,25)} = 14.4$; $p = 0.001$), but no category effect ($F_{(1,25)} = 2.3$; $p = 0.14$) or group × category interaction ($F_{(1,25)} = 3.6$; $p = 0.07$). The significant interaction was linked to the fact that patients showed slower reaction times in the verbal modality (3,738ms ± 674) than in the visual modality (3,014ms ± 732; $F_{(1,11)} = 29.2$; $p < 0.001$), whereas healthy controls had similar reaction times in both modalities (verbal: 2,016ms ± 400; visual: 2,005ms ± 373; $F < 1$).

Semantic Task: Effects of Stimulation

ANOVAs contrasted pre- and poststimulation performance by comparing left-excitatory and right-inhibitory tDCS with sham stimulation while focusing on the two principal factors of semantic processing task (modality [verbal, visual] and category [living, nonliving]). The relationship with stimulation sessions (prestimulation, poststimulation) was used as the independent variable, whereas performance accuracy and reaction times were the two dependant variables. Incorrect responses were excluded from the analyses of reaction times.

In the verbal modality, which was predominantly affected, we found that both left-excitatory and right-inhibitory stimulation improved poststimulation performance (left-excitatory: 48% ± 23 correct; right-inhibitory: 43% ± 32 correct) as compared to prestimulation (left-excitatory: 33% ± 29 correct; $F_{(1,11)} = 5.5$; $p = 0.029$; right-inhibitory: 28% ± 26 correct; $F_{(1,11)} = 6.5$; $p = 0.027$). By contrast, sham stimulation did not have any effect on performance (poststimulation: 31% ± 24 correct; prestimulation: 34% ± 27 correct; $F < 1$). Baseline performance measured during the prestimulation test session was similar for the left-excitatory, right-inhibitory, and sham condition ($F_{(2,22)} = 1.5$; $p = 0.247$). The significant effects for left-excitatory and right-inhibitory stimulation also translated into better poststimulation performance for the direct comparisons left-excitatory stimulation versus sham ($F_{(1,11)} = 17.2$; $p = 0.002$) and right-inhibitory tDCS versus sham ($F_{(1,11)} = 6.1$; $p = 0.031$). Within the visual modality, we did not find any effect of stimulation (left-excitatory prestimulation: 60% ± 32 correct; poststimulation: 60% ± 29 correct; $F < 1$; right-inhibitory prestimulation 60.1% ± 26 correct; poststimulation: 58% ± 27 correct; $F < 1$). Likewise, no effect of stimulation was found with the living category (left-excitatory prestimulation: 47% ± 26 correct; poststimulation: 51% ± 25 correct; $F < 1$; right-inhibitory prestimulation 43% ± 22 correct; poststimulation: 52% ± 23 correct; $F_{(1,11)} = 3.5$; $p = 0.089$) or with the nonliving category (left-excitatory prestimulation: 53% ± 35 correct; poststimulation: 60% ± 27 correct; $F < 1$; right-inhibitory prestimulation 51% ± 25 correct; poststimulation: 48% ± 37 correct; $F < 1$). Combining the stimuli of the two most impaired factors of the task (verbal modality and living category), we found that right-inhibitory, but not left-excitatory, stimulation improved poststimulation performance (right-inhibitory: 50% ± 22 correct; left-excitatory: 58% ± 18 correct) as compared to prestimulation performance (right-inhibitory: 34% ± 30 correct; $F_{(1,11)} = 5.1$; $p = 0.034$; left-excitatory: 48% ± 20 correct; $F_{(1,11)} = 1.5$; $p = 0.25$). Sham stimulation did not have any effect on performance (poststimulation: 45% ± 33 correct; prestimulation: 43% ± 31 correct; $F < 1$). Baseline performance measured during the prestimulation test session was similar for the left-excitatory, right-inhibitory, and sham condition ($F_{(2,22)} = 1.9$; $p = 0.166$). The significant effect for right-inhibitory stimulation also translated into a tendency for better poststimulation performance for the comparison right-inhibitory tDCS versus sham ($F_{(1,11)} = 4.2$; $p = 0.064$). There was also a significant difference for the comparison

of left-excitatory tDCS versus sham ($F_{(1,11)} = 14.8$; $p = 0.003$).

Analyses on reaction times showed that, for the living category, which was predominantly affected in sv-PPA patients, right-inhibitory stimulation speeded poststimulation responses (3,269ms ± 650), as compared to prestimulation reaction times (3,575ms ± 749; $F_{(1,11)} = 11.0$; $P = 0.007$). By contrast, sham stimulation and left-excitatory stimulation had no effects on reaction times (sham: poststimulation, 3,320ms ± 790; prestimulation, 3,342ms ± 766; $F < 1$; left-excitatory: poststimulation, 3,291ms ± 778; prestimulation, 3,385ms ± 709; $F < 1$). Baseline reaction times measured during the prestimulation test session were similar for the left-excitatory, right-inhibitory, and sham condition ($F_{(2,22)} = 2.4$; $p = 0.121$). The significant effect for right-inhibitory stimulation also translated into a tendency for faster poststimulation reaction times for the comparison of right-inhibitory tDCS versus sham ($F_{(1,11)} = 3.3$; $p = 0.096$), whereas there was no significant difference for the comparison of left-excitatory tDCS versus sham ($F < 1$). Conversely, within the nonliving category, we did not find any effect of stimulation (left-excitatory: prestimulation, 3,501ms ± 1,001; poststimulation, 3,278ms ± 825; $F < 1$; right-inhibitory: prestimulation, 3,487ms ± 696; poststimulation, 3,407ms ± 793; $F < 1$). Likewise, no effect of stimulation was found in the verbal modality (left-excitatory: prestimulation, 4,003ms ± 891; poststimulation, 3,979ms ± 693; $F < 1$; right-inhibitory: prestimulation, 3,979ms ± 675; poststimulation, 3,733ms ± 690; $F_{(1,11)} = 4.4$; $p = 0.059$) and in the visual modality (left-excitatory: prestimulation, 2,936ms ± 814; poststimulation, 2,860ms ± 913; $F < 1$; right-inhibitory: prestimulation, 3,154ms ± 808; poststimulation, 3,008ms ± 792 correct; $F < 1$). Combining the stimuli of the verbal modality and living category we found that right-inhibitory, but not left-excitatory stimulation, speeded poststimulation reaction times (right-inhibitory: 3,617ms ± 662; left-excitatory: 3,824ms ± 836), as compared to prestimulation performance (right-inhibitory: 4,052ms ± 810; $F_{(1,11)} = 8.5$; $p = 0.014$; left-excitatory: 4,017ms ± 977; $F < 1$). Sham stimulation did not have any effect on reaction times (poststimulation: 3,974ms ± 973; prestimulation: 3,993ms ± 884; $F < 1$). Baseline reaction times measured during the prestimulation test session were similar for the left-excitatory, right-inhibitory, and sham condition ($F_{(2,22)} = 2.3$; $p = 0.110$). The significant effect for right-inhibitory stimulation also translated into faster poststimulation reaction times for the comparison of right-inhibitory tDCS versus sham ($F_{(1,11)} = 5.9$; $p = 0.033$), whereas there was no significant difference for the comparison left-excitatory tDCS versus sham ($F_{(1,11)} = 2.1$; $p = 0.179$). Finally, we statistically checked for eventual retest order effects regarding performance accuracy and reaction times across the three stimulation sessions, despite the fact that our study design was conceived to avoid such biases by strictly counterbalancing the applied test versions across the twelve patients (version 1 and version 2 of the semantic test). Statistical analyses compared global prestimulation performance accuracy and response reaction times between the three stimulation sessions. They showed an absence of any retest order effects in version 1 and version 2, for both measures (performance accuracy version 1: first session, 57% ± 14 correct; second session, 58% ± 13 correct; third session, 57% ± 13 correct; $F < 1$; performance accuracy version 2: first session, 59% ± 12 correct; second session, 53% ± 17 correct; third session, 60% ± 11 correct; $F_{(2,10)} = 1.9$; $p = 0.194$; reaction times version 1: first session, 3,367ms ± 742; second session, 3,389ms ± 766; third session, 3,366ms ± 844; $F_{(2,10)} = 1.5$; $p = 0.274$; reaction times version 2: first session, 3,375ms ± 807; second session, 3,354ms ± 799; third session, 3,401ms ± 849; $F < 1$).

To summarize, significant stimulation effects were found for performance in the verbal modality (left-excitatory and right-inhibitory tDCS), for reaction times within the living category (right-inhibitory tDCS), and for both performance and reaction times in the combined verbal × living condition (right-inhibitory tDCS). At the individual level, performance in the verbal modality significantly improved (post- vs prestimulation) after left-excitatory tDCS in 10 of the 12 patients ($p < 0.05$), and there was a trend for improvement in the remaining 2 patients ($p < 0.1$, but >0.05). Performance in this modality was also significantly improved after right-inhibitory tDCS in 10 patients ($p < 0.05$), with a trend for the 2 remaining patients ($p < 0.1$, but >0.05). Within the living category, reaction times were significantly faster after right-inhibitory tDCS in 9 patients ($p < 0.05$), with a trend for acceleration in 2 patients ($p < 0.1$ and >0.05), but no significant modulation in the remaining twelfth patient ($p = 0.014$). In the combined verbal × living condition, performance was improved and reaction times were faster after right-inhibitory tDCS in 11 patients ($p < 0.05$), with a trend for 1 patient ($p < 0.1$, but >0.05). Figure 5 illustrates the gain of function attributed to stimulation as calculated by the formulas [performance accuracy poststimulation – performance accuracy prestimulation] and [reaction times poststimulation – reaction times prestimulation], showing a mean gain of 15% (±6) of accuracy in the verbal modality, of 16% (±7) in the combined verbal × living condition, and a mean gain of 306 ms (±92) with the living category and of 435 ms (±118) for the combined verbal × living condition.

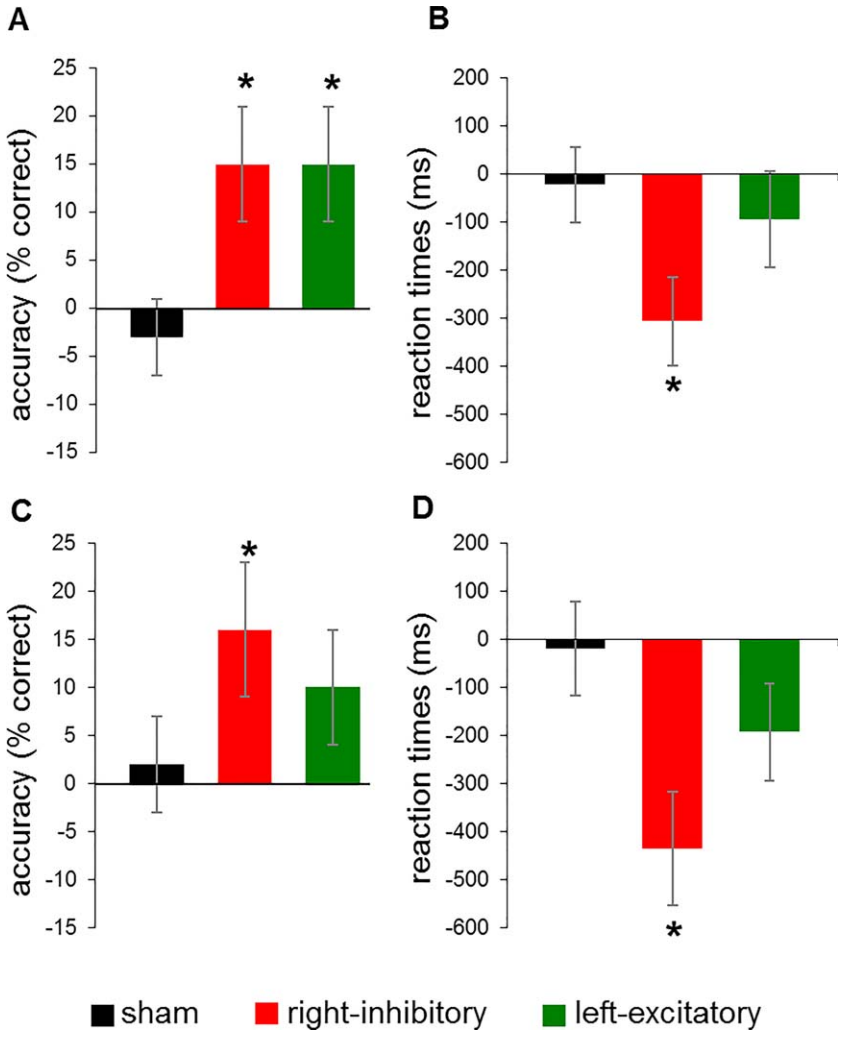

FIGURE 5: Gain of function in the semantic matching task for the post-/prestimulation contrast, comparing left-anodal-excitatory and right-cathodal-inhibitory to sham tDCS (mean values ± standard deviations). Significant gain of function for performance accuracy is observed in the verbal modality after left-excitatory and right-inhibitory tDCS (A), for reaction times in the living category after right-inhibitory tDCS (B), and for both performance and reaction times in the combined verbal × living condition after right-inhibitory tDCS (C,D). tDCS = transcranial direct current stimulation.

Discussion

Using a double-blind, sham-controlled, cross-over design in a well-characterized sv-PPA population, we assessed the effects of tDCS on semantic performance with two stimulation strategies: anodal-excitatory stimulation of the left temporal pole to boost activity in language-related semantic networks and cathodal-inhibitory stimulation to the right temporal pole to reduce activity in contralateral inhibitory networks. Our data provide evidence for a gain of function within the semantic system itself modulating the most impaired processing domains. Left-excitatory and right-inhibitory tDCS improved semantic accuracy in the verbal modality, and right-inhibitory tDCS additionally increased processing speed with living categories and boosted both accuracy and processing speed in the combined verbal × living condition.

These findings are in line with past reports suggesting that non-invasive stimulation might have beneficial effects in PPA[10–15] and confirm stimulation efficiency, for the first time, with a controlled double-blind design in the largest stimulated homogeneous PPA cohort. Our findings also extend cohort-based evidence from nonfluent PPA[13,14] to the most frequent PPA variant, sv-PPA, and refine previous stimulation approaches in PPA, primarily focusing on non-language-specific dorsolateral prefrontal cortices,[10,11,13,14] by directly targeting language/semantic-relevant cortical sites.

Targets, Processing Domains, and Stimulation Modality

An important outcome of this study is to reveal the relevance of evidence-based selection of stimulation targets, which should correspond to the anatomical coordinates of the damaged processing system and conform to the damaged cortices or contralateral regions. Following this approach, targeting temporal poles, which are known to implement semantics,[26] has yielded highly semantic-specific effects in our patient population, whereas targeting the dorsolateral prefrontal cortex in a previous report with 4 sv-PPA patients did not lead to any modulation.[13] The relevance of a stringent target-structure-function approach is also supported by studies with poststroke aphasia. Monti et al[32] have shown that tDCS applied to lexical-related left frontotemporal areas improved naming, whereas targeting the occipital cortex did not modulate language performance. Likewise, stimulation of various sites within the frontal cortex has shown that improvement in naming is associated with inhibitory TMS to the right homotopic region of Broca's area, whereas stimulation of non-language-related frontal areas had no language effect.[54,55] Despite such evidence, stimulation studies in PPA have primarily targeted non-language-specific prefrontal cortices showing, nevertheless, some effects especially on word production.[10,11,13,14] Such outcomes might be explained by the improvement of frontal-related executive functions subserving control on word retrieval[56] and/or by facilitating the activation of the nearby Broca's area through field spreading. In any case, the use of such nonspecific targets represents an indirect strategy, presumably not promoting an optimal boosting of linguistic or semantic capacities in aphasia patients.

Another key outcome of this study is that the stimulation of temporal poles selectively modulated the most impaired processing domains: verbal semantics and living categories. This result strongly suggests that tDCS was active within the semantic system itself, and that the observed intrasemantic effects are not linked to the modulation of general processes, such as attention/executive control, which might have facilitated task performance as such. It also indicates that the intrinsic activity of a given cerebral system is critical for its responsiveness to stimulation, which appears to yield greater effects for systems at low activity states. Similar results indicating selective effects for highly damaged representations and related cortical areas were found by Cotelli et al.[13] They applied TMS and a naming task in nonfluent/agrammatic PPA characterized by predominant impairment of verb as compared to noun naming.[57] Targeting prefrontal areas, which are predominantly damaged in this variant,[4] the researchers showed improvement in naming of verbs, whereas no effect was observed with less-impaired object/noun naming. A neurophysiological explanation for such selective responsiveness would be that the impact of neurostimulation depends on the state of ongoing neural activity within the target region.[58] To this regard, visual adaptation experiments have shown a predominant excitatory stimulation impact on neuronal populations engaged in low activity levels and a sparing of neuronal clusters with higher activity levels.[59] Such a state-dependency framework[58] also provides a therapeutic rationale for combining stimulation with concomitant behavioral tasks that might either enhance or reduce activity of specific networks hosted in the target region, thus maximizing the selectivity of stimulation effects and minimizing spread onto spared subsystems.

We also addressed the issue of the optimal stimulation modality comparing left-anodal-excitatory stimulation and right-cathodal-inhibitory stimulation. The latter approach, based on the rationale of interhemispheric inhibition exerted by right anterior temporal networks on the potentially left-sided semantic system, generated more-extensive effects than direct excitatory tDCS to the left hemisphere's temporal pole. This right-inhibitory advantage is also reflected in a review of stimulation investigations in poststroke aphasia showing that researchers mostly reported significant effects after inhibitory stimulation of right homotopic areas of the left-sided language network.[60] Such a difference in efficacy might relate to the fact that excitability modulations induced by neurostimulation depend on the biophysical characteristics of the target region. Computational models have shown that the electrical field induced by TMS or tDCS can be greatly distorted, in focality, distribution, and magnitude, by anatomical anisotropies and cortical thinning, resulting in subarachnoidal space enlargement and increase in the volume of conductive CSF.[61] In front of sv-PPA cases with anatomical distortions caused by cortical atrophy, stimulation-induced inhibition of the relatively less-damaged right anterior temporal cortex might therefore boost activity more smoothly in semantic-relevant areas of the left temporal pole and constitute the optimal therapeutic approach.

Finally, with regard to the effects of tDCS stimulation on semantic systems, the most plausible interpretation remains to consider that left anodal tDCS increased local activity, whereas right anodal tDCS decreased it. This assumption is based on past evidence of the local effects of anodal and cathodal tDCS on motor and visual excitability, and also on the impact of similar interventions on poststroke language disorders. Furthermore, it is also supported by computational models of tDCS current

density and flow, calculated for the stimulation montages, electrode shape, size, and locations used in the current study. Nonetheless, in the absence of a direct reliable physiological measure of tDCS impact, which could not be implemented in our study, unexpected effects, similar to those punctually reported in the human corticospinal tract (consisting in "paradoxical" facilitation following 2mA, but not 1mA, cathodal tDCS stimulation) cannot be fully ruled out.[62]

Architecture of Semantics

Our data have also implications for anatomofunctional models of semantics. Most of them stipulate that semantic representations are implemented by the temporal poles,[26,27] but there is considerable debate whether this anterior-temporal network hosts an amodal semantic system with a redundant bilateral distribution[26,63] or whether it includes distinct modality-specific subsystems dedicated to verbal or visual semantics.[24,64] A directly related issue is the left/right distinction leading to two competing proposals stipulating that the left temporal pole specifically impacts verbal semantics[5,24] or, alternatively, that such an apparent lateralization is subtended by subcortical connectivity between a bilateral amodal system and the left-lateralized language module.[27]

Our stimulation procedure, contrasting excitatory stimulation of the left and inhibitory stimulation of the right temporal pole, elucidates these issues by supporting the existence of a modality-specific network dedicated to verbal semantics located in the left temporal pole. First, our data revealed a behavioral-functional dissociation between verbal and visual semantics in sv-PPA, as reflected by significantly lower performance in the verbal modality. This result is consistent with previous findings in sv-PPA[5,25] and reinforces them by directly contrasting identical concepts in a verbal and picture format, thus avoiding biases linked to variability of "semantic familiarity." Second, our tDCS data revealed a neural-functional dissociation, as reflected by low activity states and high stimulation responsiveness for verbal-semantic networks, and unresponsive neural states for visual-semantic networks. Stimulation in sv-PPA therefore uniquely allowed for the demonstration of a neural state dissociation within anterior temporal cortices, whereas stimulation of temporal poles in healthy adults could not provide such a distinction given intact, and probably similar, neural states for verbal and visual semantics. Indeed, Pobric et al,[65] using healthy adults and a semantic matching task similar to ours, have applied inhibitory TMS to the left and right temporal pole showing significant modulation of semantic processing in both conditions, yet without any difference between verbal and visual semantics. Third, our results specify the lateralization of semantic networks by showing that boosting the left temporal pole by both left-excitatory and right-inhibitory tDCS yielded significant improvement of verbal, but not visual, semantics. This result is hardly compatible with models of bilaterally distributed amodal representations,[26,27,63] which would predict that inhibitory tDCS to the right temporal pole reduces, and excitatory tDCS to the left temporal pole improves, semantic processing as such. Contrary to this prediction, our results showed highly selective improvement of verbal semantics after both excitatory stimulation to the left temporal pole and inhibitory tDCS to the right temporal pole, probably impacting the left anterior temporal cortex through intercallosal inhibitory projections. These data add substantial evidence for the model of Mesulam et al,[24] proposing the existence of a specific subsystem for verbal semantics in the left anterior temporal cortex.

Conclusion

Our study has implications for both clinical research on therapeutic strategies in PPA and fundamental accounts on the architecture of semantics. It highlights the existence of a specific semantic network for verbal meaning. Moreover, it opens an avenue for trials in PPA using multiday stimulation regimes to promote long-lasting plasticity across language networks and drive sustained improvements in semantic processing. Such enduring outcomes, lasting for several months following the discontinuation of a noninvasive stimulation treatment, have been shown in poststroke aphasia[66] and should now be replicated in degenerative aphasia. Indeed, the "proof of concept" provided by our pretherapeutic study sets the stage for carrying out such clinical research protocols in sv-PPA patients. Further studies to be performed in parallel would be required to extend the rationale also to logopenic and nonfluent/agrammatic PPA variants. To this regard, it can be hypothesized that nonfluent/agrammatic PPA would respond to the modulation of the damaged posteroinferior frontal cortex, whereas the temporal-parietal junction would be an optimal stimulation target in logopenic PPA.

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Author Contributions

Study concept and design was done by M.T., A.V-C., M.V., and L.L. Data acquisition and analysis was done by C.L., J.G., B.D., R.L., A.K., A.B, A.V-C., DQ.T., M.B., and M.T. The manuscript was written by C.L., J.G., A.V-C., and M.T. C.L. and J.G. equally contributed to the study.

Potential Conflicts of Interest

Nothing to report.

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