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Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease

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ABSTRACT

Background: Verbal fluency relies on the coordinated activity between left frontal and temporal areas. Patients with Parkinson's disease (PD) present phonemic and semantic fluency deficits. Recent studies suggest that transcranial direct current stimulation (tDCS) enhances adaptative patterns of brain activity between functionally connected areas.
Objective: The aim of this study was to assess the differences in the effects induced by tDCS applied to frontal and temporo-parietal areas on phonemic and semantic fluency functional networks in patients with PD.
Method: Sixteen patients were randomized to receive tDCS to left dorsolateral prefrontal cortex (DLPFC) and left temporo-parietal cortex (TPC) in a counterbalanced order. Immediately following stimulation, patients underwent a verbal fluency paradigm inside a fMRI scanner. Changes induced by tDCS in activation and deactivation task-related pattern networks were studied using free-model independent component analyses (ICA).
Results: Functional connectivity in verbal fluency and deactivation task-related networks was significantly more enhanced by tDCS to DLPFC than to TPC. In addition, DLPFC tDCS increased performance on the phonemic fluency task, after adjusting for baseline phonemic performance.
Conclusions: These findings provide evidence that tDCS to specific brain regions induces changes in large scale functional networks that underlay behavioural effects, and suggest that tDCS might be useful to enhance phonemic fluency in PD.

Introduction

Verbal fluency is a classical neuropsychological measure of language production. In particular, phonemic fluency requires individuals to generate lists of words that start with a given letter, while semantic fluency involves generation of words to semantic category cues in a limited period of time [1].

In patients with focal brain lesions, impairment of both phonemic and semantic fluency has been found after frontal lobe damage [2,3]. However, some studies suggest that phonemic fluency relies on a partially different neural network than semantic fluency. For instance, frontal lobe lesions can disproportionately impair phonemic fluency [4–6], while temporal lobe damage impairs semantic fluency to a greater extent [5,7]. Functional neuroimaging studies have generally supported these findings, showing that both verbal fluency tasks are associated with activation of left frontal [8–11] and parietal areas [11,12], while semantic tasks involve additional activation of left temporal regions [11,12].

Parkinson's disease (PD) is associated with phonemic and semantic fluency deficits [13–15]. These deficits have been thought to both be caused by frontal lobe dysfunction in PD [16], but a recent meta-analysis [17] showed that PD patients present greater deficits on tests of semantic than phonemic fluency, implying that pathology in the temporal lobe might contribute to the observed

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fluency impairment. In line with this, gray matter loss in temporal and frontal areas has been found to correlate with semantic fluency deficits in PD patients [18].

Thanks to the development of non-invasive brain stimulation techniques it is now possible to modulate cognitive functions in neurological diseases such as PD. These techniques might provide clinical benefits for the patients as they appear to enhance adaptative patterns of brain activity, suppress maladaptative patterns of activity and restore equilibrium in imbalanced neural networks [19]. For instance, transcranial direct current stimulation (tDCS) can improve cognitive performance in healthy individuals and change cortical excitability in a polarity-dependent manner, with brain excitability being usually increased by anodal tDCS and decreased by cathodal tDCS [20,21]. Recent fMRI studies suggest that anodal tDCS increases brain excitability in the underlying stimulated area and distant presumably connected brain regions, suggesting that tDCS has an effect on brain functional connectivity [22–24]. In patients with PD, anodal tDCS has been shown to improve working memory when targeting the prefrontal cortex [25], and motor functions by increasing motor evoked potential amplitudes over the stimulated motor area [26].

In the current study, our aim was to assess the effects of tDCS on phonemic and semantic fluency functional networks in patients with PD. We hypothesized that tDCS to the left dorsolateral prefrontal cortex (DLPFC) or left temporo-parietal cortex (TPC) would have differential effects on phonemic and semantic verbal fluency and its associated neural networks. We evaluated changes in functional connectivity associated with left frontal and temporo-parietal brain stimulations. In addition, we also assessed the effects of tDCS on deactivation task-related pattern networks that presented high spatial correspondence with the default-mode network, since PD has been recently associated with alterations of the default-mode network [27–29]. We predicted that frontal tDCS would increase functional connectivity in both fluency networks, while temporo-parietal tDCS would increase functional connectivity specifically in the semantic fluency network. Additionally, we predicted that DLPFC tDCS would induce greater increases in functional connectivity of the deactivation network than TPC tDCS, consistent with studies showing significant effects of prefrontal tDCS on the default-mode network [30,31].

Methods

Subjects

Sixteen patients with PD were recruited from an outpatient Movement Disorders Clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona, Spain) during a three month period. Inclusion criteria to participate in this study involved: diagnosis of idiopathic PD according to the UK Parkinson's disease Society Brain Bank criteria [32]; a good initial response to L-dopa or dopamine agonists; lack of diagnostic criteria for dementia associated with Parkinson's disease [33]; and absence of clinical depression. In addition, the following exclusion criteria were applied: other brain disorders apart from PD; parkinsonism due to antipsychotic medications or other drugs; delirium; confusion; amnestic disorder; neuropsychiatric diseases; severe vascular risk factors; vascular lesions; and past traumatic brain injury on MRI. All patients gave their written informed consent to the study, which was approved by the ethics committee of the Hospital Clinic, Barcelona.

Patients were clinically assessed using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) [34] and the Hoehn & Yahr scale [35]. They were further screened for dementia and depression using the mini-mental state examination (MMSE) [36] and the Geriatric Depression Scale (GDI) [37], respectively. Moreover, they underwent a neuropsychological test battery that included: the Rey's Auditory Verbal Learning test, the Vocabulary and Letters/Digits subtests of the WAIS, a short version of the Boston Naming test and the Visual Form Discrimination test. Procedures for neuropsychological assessment are described in Lezak et al. [1]. All patients were studied while treated with levodopa alone or a combination of levodopa and a dopamine-agonist (pramipexole, ropinirole), in addition to rasagiline as monotherapy. In order to take into account the total amount of all dopaminergic drugs the patients were taking, we calculated a levodopa-equivalent dose for each patient according to procedures that have been previously described [38–41]. A detailed description on dopaminergic medication has been provided as supplementary data (Supplementary Table 1). All patients were assessed in the on phase.

Direct current stimulation (tDCS)

tDCS was delivered via a pair of water-soaked sponge electrodes (35 cm^2 surface), with an intensity of 2 mA during 20 min using a battery-driven, constant current stimulator (Phoresor, Iomed Inc., Salt lake City, UT, USA). The anode electrode was placed over F3 (left DLPFC) or P3-T5 (left TPC) according to the 10–20 international system [42], and in either case the cathodal electrode was placed over the right supraorbital area (R SO).

Image acquisition

Scanning was performed on a 3T Siemens Tim Trio MRI System (Erlangen, Germany) equipped for echo-planar imaging with a 12-channel head coil at the Center for Image Diagnosis (CDIC) of the Hospital Clinic, Barcelona. During this scan, subjects remained in the supine position with their heads immobilized by cushioned supports and a forehead strap to minimize head movement. Moreover, they wore earplugs to attenuate MRI gradient noise.

Blood oxygenation level-dependent (BOLD) functional imaging was performed using a gradient echo T2-weighted pulse sequence (TR/TE = 2000/29 ms, flip angle = 90°, FOV = 220 × 220 mm, 40 axial slices, slice thickness = 3.75, matrix = 128 × 128). To aid in the localization of functional data, a high resolution T1-weighted MPRAGE sequence (TR/TE = 2300/2.98 ms; TI = 900 ms; FOV = 256 × 256 mm; 240 sagittal slices; slice thickness = 1.0 mm; matrix = 256 × 256) was also acquired.

Experimental protocol

This study was designed as a cross-over tDCS experiment combined with fMRI. First, baseline performance in phonemic and semantic fluency tasks was assessed in all patients. The phonemic task consisted of generating words beginning with the letter P, while the semantic task consisted of producing as many names of animals as possible. For each task there was a limit of 60 s. Patients were instructed not to provide the same word twice, use the root of a word more than once or use proper nouns.

After these tasks patients were randomized to receive either left DLPFC or left TPC tDCS for 20 min and then immediately asked to perform an overt fMRI paradigm of verbal fluency inside the scanner (Fig. 1). This paradigm consisted of a block design (ABCD) where each block was formed by three periods of activation alternating with one period of rest (fixation task) that lasted 20 s each. Activation conditions consisted of overtly repeating the word "mountain" (repetition task), generating words from a given category (e.g. plants, furniture, colours – semantic fluency task) and generating words beginning with a particular letter (e.g. B, F, T – phonemic fluency task). There were six fMRI blocks and the task lasted for 8 min in total. After completing the task inside the

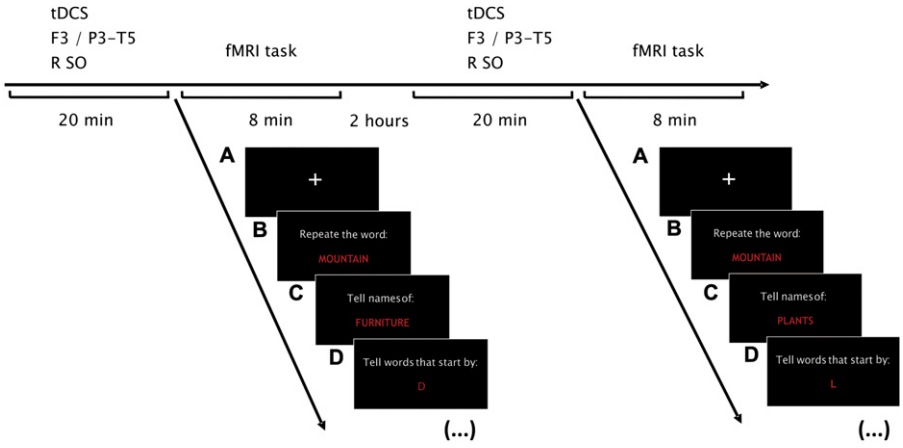

Figure 1. *Experimental procedure*. After performing the baseline phonemic and semantic fluency tests, PD patients were randomized to receive left anodal DLPFC (F3) tDCS and left anodal TPC (P3-T5) tDCS in a counterbalanced order. The cathode electrode was placed over the right supraorbital area (R SO) in both stimulation conditions. After tDCS, patients performed an fMRI verbal fluency paradigm inside the scanner, which consisted of: A) cross fixation; B) repeat continuously the word "mountain"; C) perform a semantic fluency task; D) perform a phonemic fluency task. Each of these tasks lasted 20 s and was repeated 6 times (once per block) in the first and second fMRI session. The tDCS and fMRI lasted, respectively, 20 and 8 min each.

scanner a 2 h break was given to patients to wash-out any residual tDCS effects.

Once this break was over, patients were asked to repeat the experiment. The second tDCS and fMRI paradigm were counterbalanced with respect to the first so that all patients went through both stimulation conditions and both fMRI sessions of verbal fluency. In order to control the effects of tDCS on motor functions and mood, patients performed the Purdue Pegboard test [43] and self-evaluation visual analogue scales (VAS) assessing different mood domains (nervousness, happiness, sadness, hope or pain) after each stimulation period.

Programming of the verbal fluency paradigms was carried out using the Presentation package software (Neurobehavioral Systems, 2004). Categories and letters for the semantic and phonemic fluency tasks were selected from the Lexesp-Corco database [44] and a review on categories and their rules in the Spanish language [45]. A total of 12 categories and 12 letters were selected and matched according to their difficulty in Spanish language across both fMRI sessions.

The patient's overt responses during the fMRI task were obtained via a MRI-compatible patient response and sound system, which included a microphone attached to headphones worn by the subject during the MRI scanning. Responses were recorded on a computer using Windows Media Player software at a sampling rate of 44.1 kHz. Recordings were subsequently played back for transcription using the same program.

Behavioural statistical analysis

Statistical analyses of behavioural variables were carried out using SPSS software version 16.0 (SPSS Inc., 1989–2007). To correct verbal fluency performance by the patient's articulatory abilities and speed of speech, which have been consistently reported as being impaired in PD [46–49], semantic and phonemic fluency scores were corrected by performance on the repetition task (number of words in phonemic or semantic fluency/number of times they repeated the word "mountain"). Differences in semantic and phonemic verbal fluency performance following tDCS were tested separately by means of two repeated-measures ANOVAs with stimulation condition as the within-subjects factor (two levels; fluency performance after DLPFC and TPC tDCS) and fluency performance (two levels; phonemic and semantic fluency). In this analysis, age and baseline scores on phonemic or semantic fluency were included as covariates in order to control for possible individual differences of verbal fluency abilities between patients. In addition, in order to potential order effects of the stimulations we performed ANOVAs with phonemic and semantic performance following tDCS as within-subjects factors and the order of the stimulations as a between-subjects factor. We also performed correlation analyses to assess the relationship between tDCS effects and relevant clinical variables, we performed correlation analyses using Pearson or Spearman coefficients when appropriate between scores of the UPDRS, the HY scale and daily dopaminergic dosis with semantic and phonemic fluency performance after DLPFC and TPC tDCS. Finally, patients were also divided in terms of clinical severity as reflected by the HY scale to assess potential differences of effects of tDCS between less advanced and more advanced disease stages. For all statistical analyses a $P < 0.05$ was established as a criterion for statistical significance.

Functional connectivity data analysis

To study functional connectivity we selected an independent component analysis (ICA) approach using multivariate exploratory linear decomposition into independent components (MELODIC) [50] as implemented in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) [51]. ICA is a data-driven method that extracts temporally related signals hidden within sets of random and unrelated variables. It assumes that fMRI data are linear mixtures of independent source signals that represent coherent groupings of BOLD signal change, which are often referred to as component maps and thought to be functionally relevant networks. Using different modules of FSL, the following prestatistics processing was applied to the fMRI data: motion correction [52], non-brain removal [53], spatial smoothing using a Gaussian kernel of FWHM = 8 mm, mean-based intensity normalization of all volumes by the same factor and highpass temporal filtering of 160-s. After preprocessing, images were registered to MNI space using a mean EPI image generated from all subjects and registered to the T1 image [54].

The subject's time series were then temporally concatenated into a single 4D time series and separated in 63 independent components (ICs) with automatic dimensionality estimation (the number of components to extract was determined by MELODIC). One advantage of ICA is that it automatically isolates noise-related signal fluctuations such as head motion, which is especially relevant in studies using overt speech paradigms such as our own.

Table 1
Clinical and neuropsychological data of PD patients.

	PD patients ($n = 16$)
Demographic information	
Gender (M:F)	7:9
Age (years)	61.5 ± 9.9
Education (years)	12.3 ± 6.1
Clinical data	
HY stage	1.6 ± 0.5
UPDRS	13.3 ± 5.6
MMSE	27.7 ± 2.1
GDS	6 ± 3
Dopaminergic dosis (mg)	112 ± 342
Baseline fluency data	
Phonemic	17.1 ± 4.4
Semantic	22.2 ± 4.9
Neuropsychological data	
RAVLT	
Learning	47.5 ± 11.4
Delayed recall	10.6 ± 3.3
Recognition (true positives)	13.8 ± 2.1
BNT	14.4 ± 1.4
Letters & Numbers (WAIS)	9.8 ± 2.9
Vocabulary (WAIS)	45.1 ± 12.9
VFDT	27.6 ± 3.9

Means are followed by standard deviations.
Abbreviations: HY, Hoehn & Yarh scale; UPDRS, Unified Parkinson's disease rating scale; MMSE, Mini-mental state examination; GDS, Geriatric depression scale; RAVLT, Rey's auditory verbal learning test; BNT, Boston naming test; WAIS, Weschler's Adult intelligence scale; VFDT, Visual form discrimination test.
Neuropsychological data are expressed as raw scores.

In the final stage of the analysis, post-hoc regression analyses were performed on estimated time courses and session/subjects modes. All final statistical components or spatially relevant maps were thresholded at $z < 2.3$. We selected the ICs showing significant differences between the effects of DLPFC and TPC tDCS in task-related patterns using a repeated-measures ANOVA and the general linear model contrasts: verbal fluency > repetition task, phonemic fluency > semantic fluency and semantic fluency > phonemic fluency. As a secondary analysis, we performed post-hoc regression analyses on estimated time courses and session/subject modes between verbal fluency performance and the spatial maps derived from MELODIC. This analysis was aimed at assessing potential causal relationships between behavioural performance and the functional connectivity networks identified in the repeated-measures ANOVA.

In addition, we also assessed differential effects between the two stimulations on the deactivation task-related pattern networks with spatial correspondence to the default-mode network by means of the contrast: fixation > verbal fluency. The component for this contrast was selected based on the best cross correlation matching score between our set of ICs and the ones from the large resting-state fMRI dataset of "1000 Functional Connectomes" Project, publicly available at http//:www.nitrc.org/projects/fcon_1000 [55].

Results

Behavioural data

Clinical and neuropsychological data of the sample are displayed on Table 1. As expected, we found that patients generated more words in the semantic task compared to the phonemic fluency task ($F_{(1,15)} = 15.660$, $P < 0.001$) after both stimulation conditions. Moreover, a main effect of age was found ($F_{(1,15)} = 10.217, P < 0.006$), showing that older patients performed more poorly compared to younger ones on both tasks. In order to further investigate this age effect, patients were divided into two groups according to their age. This analysis showed that older patients only differed significantly from younger ones in semantic fluency performance and not phonemic fluency, independently of the stimulation (semantic fluency after DLPFC tDCS: $t = -2.509$, $P < 0.025$; semantic fluency after TPC tDCS: $t = -2.958$, $P < 0.01$; phonemic fluency after DLPFC tDCS: $t = -1.321$, $P < 0.21$; phonemic fluency after TPC tDCS: $t = -0.073$, $P < 0.943$).

Regarding the effects of tDCS on verbal fluency, there was a significant main effect of tDCS on phonemic fluency performance ($F_{(1,15)} = 14.079$, $P < 0.002$), showing that DLPFC stimulation increased the amount of words subjects produced in response to a letter, compared to TPC stimulation, after adjusting for baseline phonemic fluency performance, time of the day of stimulation and levodopa-equivalent doses (DLPFC tDCS: 47 words ± 11; TPC tDCS: 44 words ± 10). Although no significant main effects were found for semantic fluency, we observed that patients produced more words in response to a semantic category cue after DLPFC tDCS compared to TPC stimulation (DLPFC tDCS: 57 words ± 12; TPC tDCS: 55 words ± 10; $F_{(1,15)} = 3.092$, $P < 0.102$).

In order to confirm that the effect of DLPFC tDCS on the fluency tasks was not an indirect effect of tDCS on patients' speed of speech, we assessed the effect of the stimulations on the repetition task, during which patients had to repeat the word mountain as many times as possible. Results from this analysis showed that DLPFC tDCS did not have a significant effect on word repetition compared to TPC stimulation (DLPFC tDCS: 153.2 ± 32 words, TPC tDCS: 156.6 ± 30 words; $F_{(1,15)} = 1.686$, $P < 0.215$). In addition there were no significant order effects; performance on verbal fluency tasks did not differ between the first and second session of both stimulations (DLPFC tDCS: $F_{(1,15)} = 0.081$, $P < 0.781$; TPC tDCS: $F_{(1,15)} = 1.543$, $P < 0.238$). No significant differences were found between effects of left DLPFC and TPC tDCS in other controls tasks such as Purdue Pegboard test or VAS (Supplementary Table 2).

Finally, there were no significant correlations between phonemic or semantic fluency performance after DLPFC or TPC tDCS and scores on the UPDRS, HY and dopaminergic daily doses in PD patients (Supplementary Table 3). When patients were divided according to clinical severity, no differences were found in fluency performance or demographic variables such as age between groups.

Verbal fluency network analysis

We identified three ICs that were highly correlated with the task (temporally associated with the timing of the block design paradigm for the phonemic and semantic fluency conditions) and included voxels that were positively correlated with the component time course. These task-related ICs depicted significant increases induced by DLPFC tDCS in functional connectivity compared with TPC tDCS.

The first component represented a common neural network for both verbal fluency tasks (general linear model contrast: verbal fluency > repetition) and involved mainly left fronto-parietal areas as well as the fusiform and right frontal regions (Fig. 2A, Table 2). The second component depicted increases in functional connectivity during the phonemic fluency task compared to the semantic task, in a network that involved left frontal regions, the left superior parietal lobule and right insula (Fig. 2B, Table 2). Finally, the third task-related component was associated with functional coupling increases during the semantic with respect to the phonemic task condition, amongst superior temporal, lingual, right frontal and parietal areas (Fig. 2C, Table 2).

The post-hoc regression analyses revealed that phonemic fluency performance correlated positively with the component representing connectivity increases during the phonemic task with respect to the semantic task ($z = 4.31$; $P < 0.00001$).

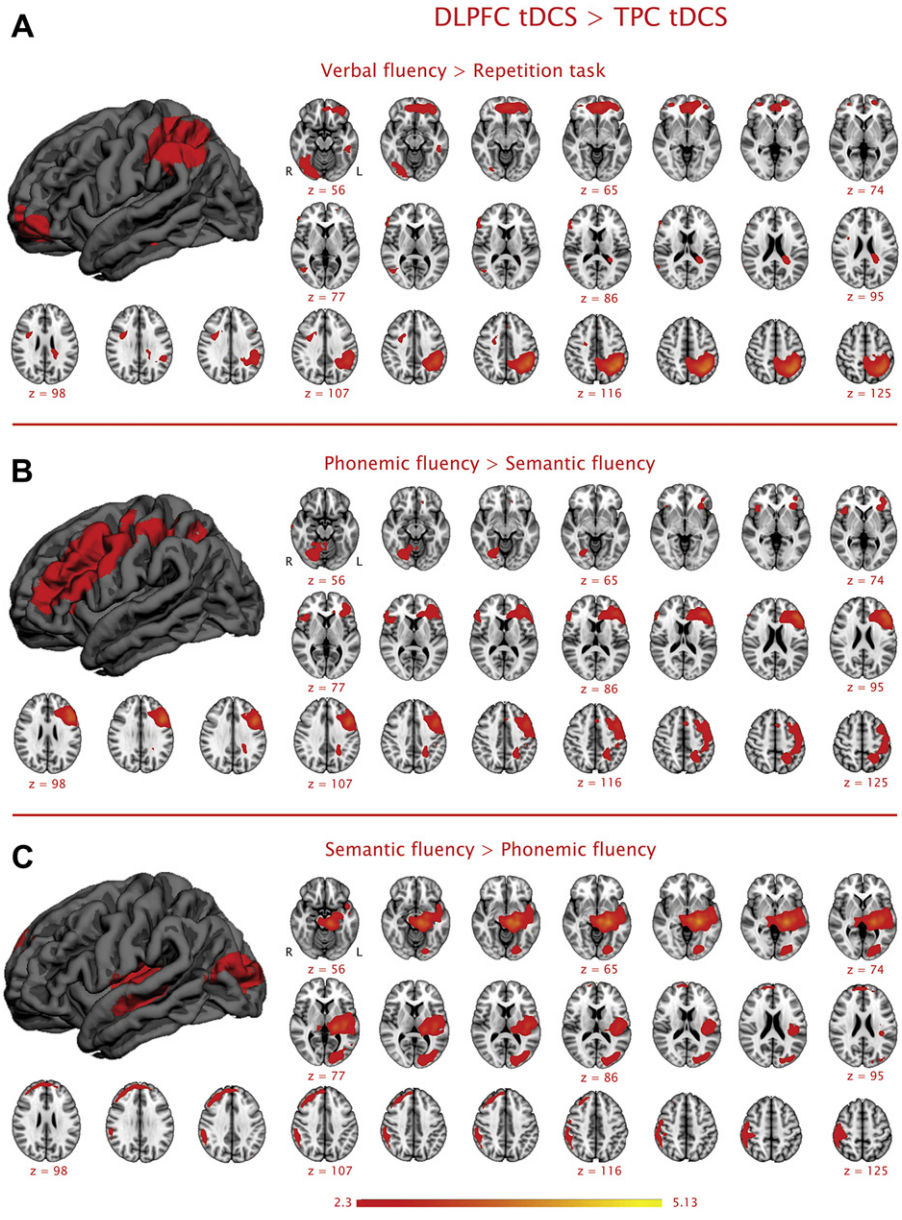

Figure 2. Functional connectivity increases induced by DLPFC tDCS compared to TPC tDCS in: (A) verbal fluency networks compared to the repetition task, (B) phonemic fluency networks compared to semantic fluency, (C) semantic fluency networks compared to phonemic fluency.

We also observed significant increases induced by DLPFC tDCS compared to TPC tDCS in the deactivation task-related pattern network (general linear model contrast: fixation > verbal fluency). This component showed functional coupling increases between the medial frontal gyrus, posterior cingulate, bilateral parietal lobules, parahippocampus, caudate, cerebellum and inferior frontal gyrus (Fig. 3, Table 3).

No components of increased functional connectivity containing activation or deactivation task-related patterns were identified after TPC tDCS compared to DLPFC stimulation.

Discussion

The main finding of this study is that tDCS enhanced functional connectivity in verbal fluency and deactivation task-related networks significantly more when applied over DLPFC than TPC in PD. In addition, DLPFC tDCS increased performance on the phonemic fluency task. These findings provide evidence of effects of DLPFC tDCS on verbal fluency networks and suggest that this technique might be useful to enhance phonemic fluency functions in patients with PD.

It has been suggested that the effects of tDCS are site specific but not site limited, spreading trans-synaptically to distant cortical structures, depending on the strength and level of activity of brain networks [56]. In this study, we found that DLPFC tDCS increased connectivity in verbal fluency networks involving frontal, parietal and fusiform areas. These findings show agreement with previous studies describing the prefrontal cortex as a crucial area for word comprehension and production [57], and parietal regions in switching between retrieval strategies [58], all processes that are essential for verbal fluency. The fusiform gyrus has also been implicated in word form processing and recognition [59]. Therefore, DLPFC tDCS increased activity in regions that have been previously associated with verbal fluency and language tasks.

Table 2
Significant increases in task-related functional connectivity induced by DLPFC tDCS compared to TPC tDCS.

Brain areas	Cluster size (voxels)	Maximal z-score primary peak	Primary peak location (mm)
Prefrontal tDCS			
Verbal fluency > repetition			
L Inferior Parietal Lobule (BA 40)	39,608	5.1	−39 −53 48
R Fusiform (BA 37)	12,917	3.19	45 −58 −20
L Middle Frontal G (BA 10)	12,409	2.87	−6 46 −4
R Inferior Frontal G (BA 46)	296	2.86	58 34 12
R Middle Frontal G (BA 10)	214	2.3	34 54 −5
L Fusiform (BA 37)	66	2.3	−50 −41 −14
Phonemic > semantic fluency			
L Inferior Frontal G (BA 9)	42,596	5.03	−46 14 28
L Superior Parietal Lobule (BA 7)	3328	3.11	−26 −54 52
R Cerebellum	2380	3.12	26 −66 −12
R Insula (BA 13)	1009	2.81	42 18 4
R Middle Frontal G (BA 46)	470	2.67	54 34 16
L Superior Frontal G (BA 6)	107	2.61	−2 18 48
L Middle Frontal G (BA 6)	76	2.41	−26 6 64
Semantic > phonemic fluency			
L Superior Temporal G (BA 22)	56,055	5.13	−50 −8 −4
R Postcentral (BA 40)	16,786	3.85	46 −31 60
L Lingual G (BA 18)	9982	2.79	−20 −80 −4
R Superior Temporal G (BA 38)	8157	4.3	38 18 −32
R Middle Frontal G (BA 8)	5090	3.1	31 42 36
L Cerebellum	1191	3.12	−14 −74 −28
R Superior Frontal G (BA 10)	25	2.3	5 64 16
R Thalamus	19	2.37	14 −30 4

Coordinates are in MNI space atlas.

Table 3
Significant increases in the deactivation task-related pattern network induced by DLPFC tDCS compared to TPC tDCS.

Brain areas	Cluster size (voxels)	Maximal z-score primary peak	Primary peak location (mm)
Prefrontal tDCS			
Fixation > verbal fluency			
R Medial Frontal G (BA 10)	101,333	7.6	6 66 12
R Caudate	9891	4.35	6 10 0
L Parahippocampal G (BA 30)	4738	2.3	−12 −39 4
R Posterior Cingulate (BA 30)	2456	3.1	8 −49 23
R Superior Parietal Lobule (BA 7)	1935	3.0	42 −66 48
L Superior Parietal Lobule (BA 7)	1346	2.44	−43 −67 45
R Cerebellum	1007	2.79	2 −62 −36
R Inferior Frontal G (BA 47)	355	2.77	34 26 −28

Coordinates are in MNI space atlas.

In addition, under the effects of DLPFC tDCS, we found functional connectivity increases in different brain areas when phonemic fluency was compared to semantic fluency. Specifically, DLPFC tDCS increased functional connectivity in phonemic networks between bilateral frontal areas, the right insula and the left superior parietal cortex. These findings agree with previous studies associating letter fluency with frontal and superior parietal areas [8,11,60]. On the other hand, DLPFC tDCS enhanced connectivity in semantic networks between superior temporal regions, the lingual gyrus and postcentral areas. These results are consistent with studies showing that semantic fluency is more related to activation of posterior cortical areas, especially of the temporal cortex [11,12]. Hence, our findings agree with the dissociation between phonemic and semantic fluency brain areas reported previously [8,11,12,60]. Furthermore, they also agree with the concept of state-dependency, according to which the effects of stimulation depend on the current state of activation of the targeted neurons [61]. For instance, in a previous study performed with transcranial magnetic stimulation [62] it was shown that while subjects were performing an ipsilateral grip motor task, DLPFC stimulation increased brain activity in the contralateral homologous area as well as in the contralateral primary motor area, whereas stimulation in a no-grip resting condition had the opposite effect. Hence, in the current study, the differential effects of DLPFC tDCS on phonemic and semantic fluency networks suggest that this stimulation increased functional connectivity between brain regions depending on the task that was being performed by the patients and their current state of brain activity.

Although we predicted that stimulation over TPC would increase functional connectivity in the semantic fluency network, our data did not show such effect. In fact, DLPFC tDCS proved to have a greater effect, by increasing functional connectivity in both verbal fluency networks significantly more than TPC stimulation. These results suggest that the left prefrontal cortex is likely to be crucial for both phonemic and semantic fluencies in PD more than temporo-parietal areas, in agreement with previous evidence suggesting that verbal fluency deficits in PD are mainly a consequence of frontal lobe dysfunction [16].

Besides modulating task-related networks, in this study DLPFC tDCS also increased functional connectivity between the medial frontal cortex, the posterior cingulate and lateral parietal areas in the deactivation task-related network, significantly more than TPC stimulation. This finding is consistent with previous studies assessing the effects of tDCS on the default-mode network. For instance, Keeser et al. [30] showed that DLPFC tDCS enhances activation in a network involving the medial frontal gyrus, anterior cingulate and the subgenual cortex during resting-state in healthy subjects. Using functional near-infrared spectroscopy, Merzagora et al. [31] came to similar findings showing oxihemoglobine increases in the prefrontal cortex during resting-state after anodal DLPFC tDCS. Finally, the magnitude of deactivation occurring in the default-mode network has been shown to correlate with better

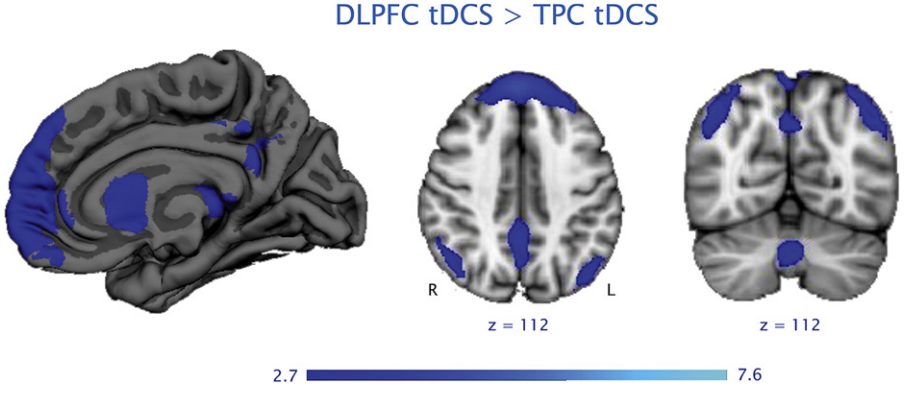

Figure 3. Functional connectivity increases induced by DLPFC tDCS in the deactivation task-related pattern network compared to TPC tDCS.

working memory performance in healthy young subjects [63]. Recent studies in PD show that these patients present reduced task-related deactivations in the default-mode network compared to healthy controls [22–24]. Hence, our results in PD agree with previous findings in healthy subjects in that anodal tDCS increases excitability of the default-mode network and suggest that these increases might contribute to normalize brain functioning and promote better task performance in PD.

In the current study, patients generated more words in the semantic fluency task than the phonemic task independently of the type of stimulation, consistent with previous studies showing higher performance in semantic compared to phonemic fluency in the general population [64–66]. In addition, we also found a main effect of age, indicating worse fluency performance in older patients compared to younger ones. However, this effect was only statistically significant for semantic fluency. This finding is in agreement with previous studies showing an age-related decline in semantic [67,68] but not phonemic fluency [69,70]. The specific decline in semantic fluency in older adults has been associated with decreases in switching abilities due to increasing deficits in executive functions that occur during aging [71]. Additionally, previous studies have shown that older subjects benefit less from the effects of non-invasive brain stimulation compared to younger ones [72,73]. Hence, the worse semantic fluency performance observed in the present study in older patients might be related to a decline both in specific cognitive functions and tDCS effects over the course of aging.

When the effects of DLPFC tDCS were compared to the ones of TPC stimulation, we found significant increases in phonemic fluency performance, after adjusting for baseline phonemic fluency abilities. This finding agrees with previous studies showing that DLPFC tDCS enhances phonemic fluency performance in healthy subjects [74,75]. In addition, phonemic fluency scores showed a positive correlation with functional connectivity increases in phonemic networks after DLPFC tDCS. This finding indicates a causal relationship between phonemic performance and phonemic network connectivity, suggesting that the functional increases induced by DLPFC stimulation led to the improvement observed on phonemic fluency performance. Although higher scores were found in the semantic task after DLPFC tDCS, this effect did not achieve statistical significance, contrary to previous reports [75]. This discrepancy could be related to a larger variability in fluency scores in our sample compared to the samples of healthy young subjects from previous studies. It is possible that when performing tDCS in neurologically impaired and older subjects, a larger sample is needed in order to observe a statistical effect of tDCS on certain tasks.

A limiting aspect of our study is the small sample size, which could have compromised the statistical power of our findings especially in relation to semantic fluency performance after DLPFC tDCS. In addition, it would have been better to collect measures of word repetition also before the stimulations, in order to further understand the effects of tDCS on more general verbal functions. Another limitation is the lack of control of varying and controlling the active electrode positions. In addition to anodal tDCS of the left DLPFC and TPC, the right supraorbital cortex was also stimulated with cathodal tDCS. Previous studies have shown that cathodal tDCS has a relevant effect on cortical activity. For instance, Lang et al., [76] reported that cathodal stimulation increased the metabolism of the cortex underlying the stimulation electrode, although these increases were much less effective compared to anodal tDCS. More recently, Stagg et al., [22] showed that the effects of cathodal tDCS were not only restricted to the stimulated area but also increased functional connectivity between distant cortical regions. Hence the bipolar electrode positions used in the current study, although consistently used by previous tDCS studies [77], may have resulted in effective modulation of two brain regions. Furthermore, there is also the possibility that the effects of both stimulations interacted as they were performed on the same day. In a previous study by Monte-Silva et al., [78], it was shown that when a second cathodal stimulation is performed three hours after the first stimulation, there is a prolongation of tDCS-induced excitability decreases, which can last for a period equal or inferior to two hours. Hence, it is possible, that at least part of the behavioural effects observed in the current study, might be reflecting an interaction between the two stimulations or the joint effect of both of them. In addition, it would have been ideal to perform both DLPFC and TPC stimulations at the exact same time of the day in order to assure that dopaminergic concentration was identical as much as possible. Future studies assessing the effects of two active stimulations at the same time of the day and on different days will be required in order to confirm the findings from the current study.

Although previous studies have suggested that tDCS effects on cortical activity can last for 1 h or longer when applied for 10 min [20], recent studies using neuroimaging techniques show that the influences of this stimulation on brain activity are in fact limited to 10 min [30] or 15 min at the most [31], disappearing completely once this time interval has elapsed. Taking into account the above-mentioned studies, the counterbalanced study design, and the fact that we found significant effects of DLPFC tDCS both at a behavioural and functional connectivity level compared to TPC stimulation, we do not think that performing both stimulations on the same day 2 h apart confounded our results. Finally, the fact that we did not include a sham stimulation condition in the current study makes it impossible to exclude an order effect of performance, as compared to baseline values. However, the additional analyses that were carried out showed no significant differences between the first and second sessions on verbal fluency, reducing the probability of a potential order effect in the present findings.

In summary, our study provides the first evidence of tDCS-induced changes in activity in large scale brain networks in patients with PD. Our findings extend previous evidence in healthy subjects showing connectivity increases in activation and deactivation task-related patterns after anodal stimulation of the DLPFC [30,31]. Moreover, our findings suggest that the functional connectivity increases induced by DLPFC stimulation in phonemic fluency networks led to the significant performance increases observed in this task, although future studies would be needed in order to confirm such causal relation between the observed neurobiologic and behavioural effects.

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Conflict of interest

None declared.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.brs.2012.01.006.

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