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Effects of tDCS on executive function in Parkinson's disease

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HIGHLIGHTS

- tDCS in this population of subjects is not associated with adverse effects.
- There was a specific tDCS effect on executive function.
- Dorsolateral prefrontal tDCS is not associated with motor function improvement.

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ABSTRACT

Non-motor symptoms in patients with Parkinson's disease (PD) are often poorly recognized, significantly impair quality of life and cause severe disability. Currently, there is limited evidence to guide treatment of associated psychiatric and cognitive problems. Non-invasive brain stimulation techniques have emerged as non-pharmacological alternatives to target cognitive symptoms without worsening motor function. In this context, we conducted a multicenter, sham controlled, double-blinded study to assess the immediate and long-term effects of ten consecutive sessions of transcranial direct current stimulation (tDCS) over the anode on the right dorsolateral prefrontal cortex (DLPFC) ($n = 5$), left DLPFC ($n = 6$) or sham ($n = 7$). We assessed cognitive functions, depressive symptoms and motor functions in 18 PD patients at baseline, at the end of the 2-week stimulation sessions and at 1-month follow-up. Our results showed that active stimulation of both left and right DLPFC resulted in prolonged improvements in Trail Making Test B, an established test to measure executive function, compared to sham tDCS at the 1-month follow-up. These results suggest the existence of a beneficial long-term effect on executive functions in PD patients following active tDCS over the DLPFC. Thus, our findings encourage further investigation exploring tDCS as an adjuvant therapy for cognitive and behavioral treatment in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by gradual impairment of affective, cognitive and motor function [1]. Although motor symptoms such as resting tremor, bradykinesia, rigidity and postural instability are the hallmark of this disorder, cognitive and psychiatric non-motor symptoms (NMS) are equally disabling and directly impact the quality of life (QOL) of patients with PD [2]. In fact, recent reports show that even after controlling for duration and severity of motor symptoms, cognitive abilities, such as executive and visuospatial functions, remain positively associated with QOL [3]. Furthermore, psychiatric comorbidities, namely depression, consistently emerge amongst the strongest determinant of health related QOL in this patient cohort [4]. For these reasons, there is growing interest in treating and managing neuropsychiatric symptoms in patients with PD [5].

Cognitive functions are predominantly executed by the cortex, where dopamine is known to play a key role [6]. It has been suggested that impairment of cognitive function is related to a disruption of the dopaminergic system [7], which is also severely affected in PD. In fact, cognitive deficits in Parkinson's disease are similar to a dysexecutive syndrome. Depression, a common co-morbidity in PD, is also suggested to be caused by changes in dopaminergic transmission and alterations in excitability and

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imbalance between the left DLPFC (L-DLPFC) and right DLPFC (R-DLPFC) [8].

Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have shown to be safe and effective methods for improving cognitive and affective functions [9]. TDCS applied with the anode over the L-DLPFC and the cathode over the right supraorbital region, can improve working memory in healthy subjects [10], as well as improve mood in patients with major depression [11,12]. In this context, several studies have documented the beneficial effects of TMS and tDCS on behavioral and cognitive symptoms in PD [13–16] without worsening motor symptoms [17].

These results support the idea that active stimulation of the DLPFC with tDCS could have beneficial, lasting effects on both affective and cognitive domains in patients with PD. Therefore, we conducted a two-site, double-blind, sham-controlled, 10-session tDCS study in patients with PD. We hypothesized that tDCS applied over the L-DLPFC would improve cognitive function and affective symptoms without altering motor function when compared to sham stimulation.

2. Materials and methods

2.1. Subjects

Eighteen patients (6 women and 12 men) aged between 40 and 71 years (mean age 61 ± 8 years) with idiopathic PD were enrolled in the study. Inclusion criteria included a clinical diagnosis of PD defined by the presence of at least two out of three cardinal motor features of PD (resting tremor, rigidity, and bradykinesia, plus a sustained and significant response to dopaminergic treatment), age of 40 and over, and stable maintenance of their medication at least 30 days prior to enrollment and throughout the study. Exclusion criteria included any contraindications to tDCS, history of seizures, substance abuse, dementia, major head trauma or psychotic symptoms. The study was conducted at two centers: The Berenson-Allen Center for Non-invasive Brain Stimulation at Beth Israel Deaconess Medical Center and the Neuromodulation Center at Spaulding Rehabilitation Hospital, in Boston. A multicenter protocol was implemented at both sites. The study was reviewed and approved by the Institutional Review Boards of both centers and written informed consent was obtained from all participants.

2.2. Experimental protocol

Subjects were randomly assigned to one of the three groups in a ratio of 1:1:1 with the use of permuted-block randomization. Group 1 received tDCS with the anode over the L-DLPFC and the cathode over the right supraorbital region; Group 2 received tDCS with the anode over the R-DLPFC and the cathode over the left supraorbital region, and Group 3 received sham tDCS with two electrodes placed randomly over the L-DLPFC or R-DLPFC and the corresponding contralateral supraorbital area. Each group received a total of 10 stimulation sessions over 2 weeks (Monday–Friday) with a 2-day break during the weekend. Cognitive, affective and motor assessments were completed at baseline (visit 1), at the end of the stimulation sessions (visit 11), and at follow-up visit at 1 month (visit 12). Outcome assessors were unaware of group assignments.

2.3. Transcranial direct current stimulation

Direct current was delivered through a 1 × 1 tDCS low-intensity stimulator (Soterix Medical Inc., New York, NY) and the Chattanooga Ionto device (Chattanooga Ionto™ iontophoresis system, Chattanooga Medical Supply Inc., Chattanooga, TN) via a pair of saline-soaked electrodes (35 cm^2). For stimulation of the DLPFC, the anode was placed over F3 or F4 according to the 10–20 international system for EEG placement for L-DLPFC or R-DLPFC stimulation respectively with the montage described above. During active tDCS, a constant current of 2 mA was delivered for 20 min. For sham stimulation current was applied only for the initial 30-s ramp up and 30-s ramp down. A questionnaire was administered following each session to monitor for possible side effects.

2.4. Assessments

2.4.1. Cognitive assessments

To assess cognitive function, we used several neuropsychological tests targeting different cognitive areas of known difficulty for patients with PD. To test executive function we used Trail Making Tests A & B (TMTA & B), Wisconsin Card Sorting Test (WCST), Probabilistic Classification Learning (PCL), Working Memory Test (WM) and Stroop Test. For visuospatial ability we used the Hooper Visual Organization Test (HPVOT), and for abstract reasoning, Colored Progressive Matrices (CPM). Working memory was assessed using the forward and backward Digit Span Tests and 3-back Test. These tests have been previously used to assess the effects of rTMS in patients with PD [15]. In addition, a Mini Mental Status Examination (MMSE) test was administered during the first visit in order to obtain baseline levels of cognitive functioning.

2.4.2. Behavioral assessments

Mood/affective assessments included the Beck Depression Inventory (BDI), a 21-question multiple choice self-reported questionnaire; the Hamilton Rating Scale for Depression (HRSD), a 21-question multiple choice rater-scored scale; and the Hamilton Anxiety Scale (HAS), a scale of 14-question for assessing severity of anxiety symptoms. These scales were previously used in assessments of effects of rTMS on affect in patients with PD [16].

2.4.3. Motor assessments

For motor function assessments, the following tests were administered: Unified Parkinson's Disease Rating Scale Part-III (UPDRS-III), Simple Reaction Time (SRT) (right and left hand), 4-Choice Reaction Time (4-CRT) (right and left hand), Purdue Pegboard Test (PPT) (right and left hand), Finger tapping (FT) (right and left hand), walking time (WT), buttoning-up (BU) and supination–pronation (SP).

2.5. Statistical analysis

Statistical analyses were performed using STATA/IC 12 (StataCorp LP, TX, USA). We used intention-to-treat analysis with last observation carried forward as an imputation method. Between group differences in demographics and baseline values were compared using a one-way ANOVA for continuous variables and Fisher's exact test for categorical variables. Since we anticipated a differential effect during stimulation vs. follow-up, we divided these two periods as: (i) tDCS treatment and (ii) follow-up. Thus, analyses took into account this differential effect. We ran models using a two-part linear spline function, which allowed us to analyze slopes at these two different time points. For group comparisons we performed ANCOVA models comparing differences across groups and controlled for baseline values. Correlations among cognitive, affective and motor functions were assessed by pairwise correlation tests.

3. Results

Eighteen patients were included in the study: six patients were randomly assigned to the L-DLPFC group, five patients to the R-DLPFC group, and seven patients to the sham tDCS group. The mean

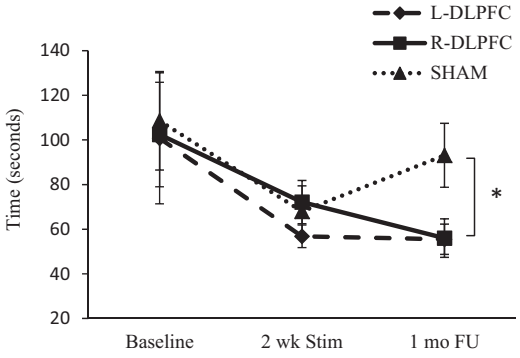

Fig. 1. Mean time (seconds ± SEM) required to complete the Trail Making Test B at baseline, after 2 weeks of tDCS stimulation and at 1-month follow-up. There was a significant difference at 1-month follow-up between sham and active groups (L-DLPFC and R-DLPFC) ($p < 0.05$). *Statistically significant.

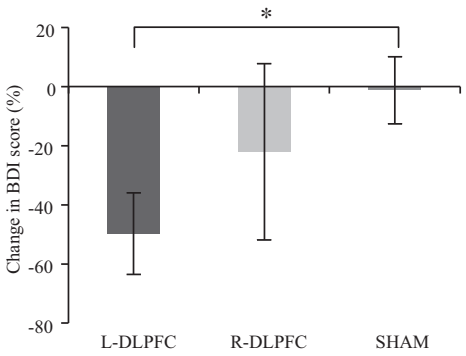

Fig. 2. Percent change in BDI score (mean ± SEM) between baseline and after 2 weeks of tDCS stimulation. There was a significant reduction in BDI scores in the L-DLPFC group when compared to sham ($p < 0.05$) (L-DLPFC = −49.8%, R-DLPFC = −22.1% and SHAM = −1.28%). *Statistically significant.

baseline MMSE score for all groups was 29.2 ± 0.3 (mean ± SEM). There was no significant difference between groups in demographics or in any of the cognitive, affective, or behavioral measures at baseline (all $p > 0.05$). The most common side effects reported were tingling (50%), sleepiness (55%) and mild headache (22%). Other side effects included neck pain (11%), skin redness (22%) and trouble concentrating (22%). None of the patients reported unexpected or severe adverse effects.

3.1. Cognitive effects

3.1.1. Trail Making Test B (TMT-B)

This analysis shows that, while all groups showed an improvement in TMT-B performance immediately following 10 days of tDCS, only the active tDCS groups showed a maintained improvement in performance at the 1-month follow-up as further detailed (Fig. 1). In our analysis, we assessed the effects based on two different time periods; (i) tDCS treatment and (ii) follow-up. We initially conducted a model using a spline transformation by taking the end of the last stimulation session as the knot for this model. Our results showed:

(i) *tDCS treatment*: There was a significant main effect of time for the first period (baseline to end of stimulation session – tDCS treatment period) (beta coefficient of −38.54 s, $p = 0.006$). To analyze the group effect we conducted an ANCOVA model adjusted for baseline values. In this model, no group differences for the tDCS treatment period were found ($p = 0.49$, effect size for group; $eta^2 = 0.02$, percent change $eta^2 = 7.75$, partial $eta^2 = 0.03$), indicating that improvement in TMT-B performance was similar among groups.

(ii) *Follow-up period*: No main effect of time was found for this period (beta coefficient of 43.76 and had only a trend for significance, $p = 0.064$), indicating no improvement on performance during the follow-up period. However analysis of group effect with ANCOVA showed significant effect of group. ($p = 0.02$, effect size for group; $eta^2 = 0.15$, percent change $eta^2 = 22.19$, partial $eta^2 = 0.32$). In fact, comparison of sham group vs. both active tDCS groups showed a significant difference ($p < 0.001$) (sham group: 25.3 s ± 19.5; active group: −8.7 s ± 6.2) indicating that the groups had differential retention effects. While both active groups retained their improvement in TMT-B performance, sham tDCS group's performance returned to baseline levels.

(iii) *Baseline vs. follow-up*: Finally, to assess the overall improvement among groups, we conducted an ANCOVA model comparing baseline vs. follow-up period and also found significant effects ($p = 0.03$; mean difference between follow-up and baseline; L-DLPFC = 45.25 s ± 59.83; R-DLPFC = 46.41 s ± 39.34 and sham group = 15.45 s ± 57.97, effect size for group; $eta^2 = 0.25$, percent change $eta^2 = 64.68$, partial $eta^2 = 0.29$), showing that while the active groups maintained the positive effects, the sham tDCS group lost most of this effect at 1-month follow-up and returned to baseline levels.

Other cognitive tasks including, WSCT, PCL, WM, CPM, HVOT, STROOP, and Digit Span showed no significant *post-tDCS* vs. *follow-up* effects when comparing across groups of stimulation.

3.2. Mood effects

ANCOVA models showed no significant effect found with spline functions. However, considering previous findings regarding changes in BDI following active tDCS [16], we ran individual exploratory tests within each group comparing the percentage of the change from baseline across groups. We found that the L-DLPFC group showed greater reduction in BDI scores (mean % reduction ± SEM: −49.8% ± 13.82) than sham (−1.28% ± 11.34) and R-DLPFC (−22.1% ± 29.82) group at the end of stimulation. (Fig. 2) This was only significant between the L-DLPFC and sham groups (Mann–Whitney test, $p = 0.027$).

3.3. Motor effects

Analyses of tests pertaining motor functions (supination–pronation, buttoning-up, finger tapping, walking time, purdue pegboard, reaction time and motor part of UPDRS) failed to show any significant effects of stimulation (all $p > 0.05$). This suggests that motor function neither improved nor declined throughout the study.

3.4. Correlations

Pairwise correlation tests with Bonferroni correction for the two significant outcomes (BDI and TMT-B) showed no significant association between any of the paired analyses.

4. Discussion

In this study we assessed the effects of tDCS with the anode over the L-DLPFC or R-DLPFC on a wide range of cognitive, affective and motor functions in patients with PD. We found that anodal tDCS over both L-DLPFC and R-DLPFC showed a significantly lasting improvement specifically in TMT-B performance when compared to sham.

Beneficial effects of tDCS on cognitive function have been shown in healthy subjects and in other neuropsychiatric conditions [9–12]. However, only a few studies have investigated the effects of tDCS on cognitive symptoms in patients with PD [14]. Our study is the first to show long lasting effects of tDCS on cognitive function in PD as measured by TMT-B. This test provides a measure of executive functions such as mental flexibility, graph motor speed, letter sequencing and mental double tracking [18].

It is important to discuss the results of this study in terms of main and simple effects. We showed a significant time effect for the tDCS treatment period without any group effect. This indicates all groups had similar improvement in TMT-B, which can be attributed to a learning effect. Although these results contradict the findings by Boggio et al. [14], who showed that anodal tDCS over L-DLPFC was associated with a significant improvement on working memory immediately following stimulation, we must note methodological differences between study designs. Boggio et al. [14] administered their cognitive tests during the stimulation session, whereas in our study tests were administered after the stimulation. It is known that mechanisms through which tDCS shows its effect are different for online and offline periods of stimulation. Online effects of tDCS are related to changes in polarization in neural membranes, whereas offline effects involve more complex processes such as long-term potentiation (LTP) and long-term depression (LTD) that lead to induction of long-term synaptic plasticity [19–21]. In fact, our results in the follow-up period were consistent with the offline effects of tDCS.

In the follow-up period we found a significant effect of group as compared to both baseline and tDCS treatment period indicating different retention effects between groups. In the active tDCS group, initial improvement following tDCS treatment was maintained, whereas in the sham group it returned to baseline. Similarly, in a study by Floel et al. [22], prolonged tDCS effects were found in other cognitive domains in elderly subjects. There was no difference between sham and active group immediately after the stimulation indicating a learning effect in both groups, but improved recall after 1 week only in the active group, suggesting a retention effect. Moreover, Jeon et al. [23], demonstrated that 1 mA tDCS over the L-DLPFC and R-DLPFC had lasting effects on measured cognitive functions for 2 weeks.

Although tests measuring other executive functions such as WCST, Stroop, and N-Back tests have been found to be helpful to measure cognitive changes in PD patients, TMT-B was the only test that showed significant changes. Similar to this result, Moser et al. [24], demonstrated that five sessions of rTMS over the L-DLPFC showed improvement only in TMT-B, but not on other neuropsychological assessments (Stroop Test, Memory or Visuospatial tests). A possible explanation to why other tests may have failed to show retention effects is the concurrent depression and anxiety. It has been shown that mood disorders can cause secondary cognitive deficits and interfere with the performance of the tests [25]. Moreover a recent study by Misdraji and Carlton [26] showed that anxiety and depression were poorly correlated to TMT-B testing which emphasizes the strong potential in using the TMT-B to assess cognitive functions in depressed individuals. Our correlational analyses did not show a significant relationship between TMT-B and affective functions (HAM-A, HAM-D, BDI) or motor functions at any time. Furthermore, in a recent review, Bossers et al. [27], compared different neurophysiologic tests used in interventional clinical trials to measure treatment effect in dementia and recommended the use of TMT-B in the assessment of executive functions given its feasibility and use in high quality randomized clinical trials (RCTs).

In addition to cognitive functioning, we also noticed improvements in depressive symptoms following L-DLPFC stimulation at the end of the 10-session intervention. Studies have shown that L-DLPFC stimulation by high frequency rTMS [28] or anodal tDCS are effective in reducing depressive symptoms [11,12]. In contrast to these studies, the subjects in this study did not exhibit significant depression scores at baseline, and thus there was less opportunity to observe potential reduction of these symptoms. Nonetheless, results found in the L-DLPFC group in favor of an antidepressant effect after 10 days of stimulation supports the findings in the literature.

Motor symptom effects were consistent with a previous trial by Fregni et al. [29]. They found that anodal tDCS over the L-DLPFC does not induce a significant reduction in motor symptoms measured by reaction time and UPDRS. As expected, and also from a safety point of view, there was no significant change in motor functions or worsening of motor symptoms. For this reason, it is unlikely that the effects found in the TMT-B simply represent changes in movement speed.

There are several limitations to our study. Use of traditional neurophysiologic measures to assess treatment effects might lack sensitivity and might be insufficient to provide information about functional improvement. However, TMT-B has been previously used in clinical trials measuring treatment effects [27] and used to predict clinical outcomes such as conversion from mild cognitive impairment to Alzheimer disease [30]. Therefore, future studies in PD should explore the use of other instruments to measure the effects of tDCS on cognition.

One important aspect to take into account is the high placebo response rate seen in PD patients. It has been shown that the placebo response in tDCS trials might be higher than the placebo response in pharmacological trials [31]. Although all of our subjects were naive to tDCS, recent studies have shown that blinding with 2 mA might not be as effective since both subjects and researchers were able to distinguish active vs. sham tDCS in crossover trials [32]. Although Palm et al. [33] found that healthy subjects were not able to distinguish between active and sham in prefrontal tDCS trials, the reliability of these blinding methods have not been investigated in patients with PD. An additional pitfall to this study might be the small sample size and the lack of power to detect a difference between groups. Thus, larger randomized-controlled trials are needed.

5. Conclusions

Results of this exploratory study suggest that anodal tDCS over the prefrontal cortex might enhance certain executive functions in PD without worsening of motor or mood symptoms. Further studies are needed to determine if there is a topographic specificity to the effects of tDCS on the various symptoms in PD, and whether these effects can be sustained when used as a co-adjuvant to pharmacological treatment.

Conflict of interest

None declared.

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