RESEARCH ARTICLE

Mild Cognitive Impairment in Parkinson's Disease Is Improved by Transcranial Direct Current Stimulation Combined With Physical Therapy

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ABSTRACT: Background: Parkinson's disease (PD) is characterized by both motor and cognitive deficits. In PD, physical exercise has been found to improve physical functioning. Recent studies demonstrated that repeated sessions of transcranial direct current stimulation led to an increased performance in cognitive and motor tasks in patients with PD.

Objectives: The present study investigated the effects of anodal transcranial direct current stimulation applied over the dorsolateral prefrontal cortex and combined with physical therapy in PD patients.

Methods: A total of 20 patients with PD were assigned to 1 of 2 study groups: group 1, anodal transcranial direct current stimulation plus physical therapy (n = 10) or group 2, placebo transcranial direct current stimulation plus physical therapy (n = 10). The 2 weeks of treatment consisted of daily direct current stimulation application for 25 minutes during physical therapy. Long-term effects of treatment were evaluated on clinical, neuropsychological, and motor task performance at 3-month follow-up.

Results: An improvement in motor abilities and a reduction of depressive symptoms were observed in both groups after the end of treatment and at 3-month follow-up. The Parkinson's Disease Cognitive Rating Scale and verbal fluency test performances increased only in the anodal direct current stimulation group with a stable effect at follow-up.

Conclusions: The application of anodal transcranial direct current stimulation may be a relevant tool to improve cognitive abilities in PD and might be a novel therapeutic strategy for PD patients with mild cognitive impairment. © 2016 International Parkinson and Movement Disorder Society

Key Words: tDCS; Nonpharmacological treatment; Noninvasive brain stimulation; Motor abilities; Frontal lobe

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease exceeded only by Alzheimer's disease (AD).[1] Clinically, PD is characterized by rest tremor, rigidity, bradykinesia, gait impairment, postural instability, motor disturbances, cognitive impairment, mood disorders, and sleep dysfunction often occur during the disease course.[2-6]

Recently, epidemiology and clinical studies have identified a new nosological entity in PD called *Mild Cognitive Impairment* (MCI). Patients with PD-MCI present subtle cognitive dysfunctions, such as memory deficits and difficulties in frontal/executive abilities, with preserved activities of daily living.[7] This condition is associated with a higher risk of developing Parkinson's dementia[8] and represents one of the most dreaded complications of the disease for patients and caregivers, occurring in about 25% of cases.

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TABLE 1. Demographic and clinical features of the sample grouped according to randomized treatment procedure [mean (SD)]

	AtDCS plus physical therapy (n = 10)	PtDCS plus physical therapy (n = 10)	*P* Value
Age, years	69.0 (9.1)	69.1 (5.6)	0.678
Education, years	8.2 (3.8)	8.9 (2.9)	0.496
Age of onset, years	62.8 (10.2)	61.3 (5.9)	0.226
Duration of disease, years	7.1 (3.6)	7.8 (4.2)	0.678
Gender, male/female	4/6	7/3	0.369[a]
Edinburgh Handedness Inventory, %	90.8 (16.2)	93.4 (9.5)	0.762
Hoehn and Yahr Scale	2.2 (0.6)	2.3 (0.4)	0.850
Unified Parkinson Disease Rating Scale–Total	50.4 (16.4)	52.4 (19.4)	0.910
Unified Parkinson Disease Rating Scale–III	27.8 (13.9)	27.6 (8.9)	0.940
Levodopa Equivalent Dose–LED, mg/day	524.6 (179.1)	815.7 (590.9)	0.345
Most affected body side, right/left	5/5	5/5	1.000[a]
Cumulative Illness Rating Scale–Severity	1.6 (0.2)	1.8 (0.2)	0.055
Cumulative Illness Rating Scale–Comorbidity	2.9 (1.1)	4.1 (1.4)	0.082

P value column reports nonparametric Mann-Whitney test.
[a]Chi-square test.

The evidence highlights the potential importance of including physical therapy as an adjuvant to pharmacological and neurosurgical treatments for PD.[9-22]

Currently there is growing interest in the application of transcranial direct current stimulation (tDCS) as an additional therapeutic approach in neurological disorders because its effects have been shown to outlast the stimulation period itself.[23-26] It has also been shown that a single tDCS session can improve cognitive and motor impairment in PD patients.[27-33]

Interestingly, recent studies in PD patients have shown that repeated sessions of anodal tDCS (AtDCS) led to an increased performance in both cognitive[34] and motor tasks with stable effects at 1-month or 3-month follow-up.[35,36] Remarkably, no studies have explored the long-term effects of repeated sessions of tDCS when combined with physical therapy in PD patients (see Supplemental Table 1).

In the present work, we sought to investigate whether repeated sessions of AtDCS may induce long-term motor and cognitive improvement if applied as an addition to physical therapy. Recent studies have described the potential beneficial effect of motor exercise in improving both cognitive and motor functions in individuals with mild to moderate PD.[37] We conducted a 2-week double-blind study with tDCS over the dorsolateral prefrontal cortex (AtDCS combined with physical therapy vs. placebo tDCS combined with physical therapy) contralateral to the most affected body side during physical therapy. Motor and cognitive performances were assessed with a standardized protocol before and after intervention, and we evaluated the persistence of the effects 3 months after the end of treatment. We hypothesized that the combined treatment of AtDCS during physical therapy would ameliorate cognitive abilities and motor symptoms associated with PD more than placebo tDCS during physical therapy.

Methods

Participants

A total of 20 PD patients were recruited for the study. All of the patients fulfilled the UK Parkinson's Disease Brain Bank criteria for the diagnosis of idiopathic PD.[38]

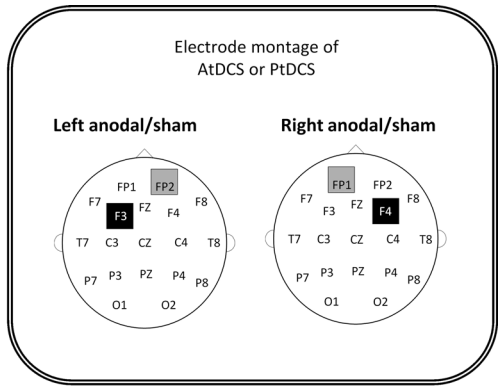
PD-MCI is a syndrome defined by clinical, cognitive, and functional criteria. The motor disability was evaluated using the motor examination section of the UPDRS-III and using the Hoehn and Yahr Scale (range: 1–3). Medical comorbidity was assessed by the Cumulative Illness Rating Scale. At the time of recruitment, all of the patients were treated with levodopa and/or dopamine agonists and received stable therapy throughout treatment. Patients were always tested in the *on* phase. Demographic and clinical characteristics are reported in Table 1. PD patients were classified according to the cut-off scores of the Parkinson's Disease Cognitive Rating Scale (PD-CRS) total score (PD-MCI = score 65–81, PD-dementia [PD-D] = score $\leq$ 64, and PD normal cognition [PD-NC] = score $\geq$ 82).[39]

Stringent exclusion criteria were (a) confounding neurological and psychiatric disorders; (b) history of traumatic brain injury; (c) clinically known hearing or vision impairment or a past history of alcohol abuse; (d) clinical presentations suggestive of dementia with Lewy bodies, progressive supranuclear palsy, multiple system atrophy, or vascular parkinsonism; (e) diagnosis of PD-D[5]; (f) implanted metal objects; and (g) a history of seizures or any contraindication to tDCS.[40]

Patients who scored below 26 of 30 total on the Mini Mental State Examination were also excluded.[41] All of the participants were made fully aware about the aims of the research, and written informed consent was acquired from all participants. The study was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration.

A)

	Number of patients	Treatment approach
Group 1	10	AtDCS during Physical Therapy *(DLPFC, 2mA, 25 min Current density 0.06 mA/cm2)*
Group 2	10	PtDCS during Physical Therapy



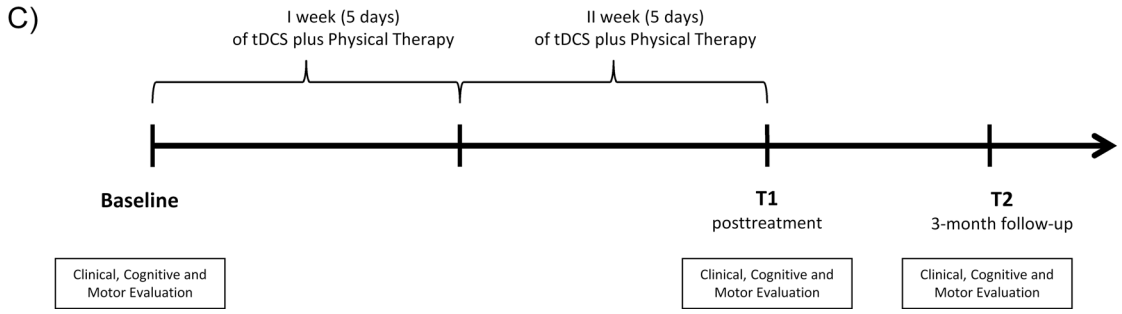


FIG. 1. A: Patient randomization in the 2 experimental groups. Physical therapy was administered during transcranial Direct Current Stimulation (tDCS) for 2 weeks, 25 minutes per day, 5 days per week. **B**: tDCS montage on dorsolateral prefrontal cortices. **C**: Experimental therapy protocol of transcranial direct current stimulation plus physical therapy.

Study Design

Through a covariate adaptive randomization method for balancing age and side of stimulation variables, the 20 enrolled PD patients were assigned to 1 of 2 treatment groups (AtDCS plus physical therapy or placebo tDCS [PtDCS] plus physical therapy).[42] All of the participants underwent 25 minutes of physical therapy conducted by a physiotherapist during tDCS treatment (either AtDCS or PtDCS) on a daily basis (5 days/week) for 2 weeks. The study was conducted in a double-blind manner to minimize potential biases from investigators and patients.

Neuropsychological and Clinical Assessment and Motor Function Evaluation

Two trained neuropsychologists who were blinded to patient treatment allocations administered the neuropsychological and clinical testing, which were divided in 2 sessions. All of the patients underwent neuropsychological and clinical assessments and a motor function evaluation before treatment (baseline, T0), 2 weeks after treatment (posttreatment, T1), and 3 months after treatment (follow-up visit, T2). See Figure 1 for details. All of the assessments for a single patient were delivered by the same assessor throughout the study.

We administered the PD-CRS, a PD-specific cognitive battery designed to cover the full spectrum of cognitive deficits (frontal-subcortical and cortical scores) associated with PD.[39]

The clinical evaluation included the UPDRS-III, the Hoehn and Yahr Scale, the Beck Depression Inventory-II (BDI-II), the Parkinson's Disease Quality of Life Questionnaire-39 (PDQ-39), and the REM Sleep Behavior Disorders Screening Questionnaire (RBDSQ).[43-45] Finally, an evaluation of motor function has been included.[46-49] The results are reported separately for the 2 experimental groups in Table 2.

Physical Therapy

Physical therapy was carried out by a therapist blinded to group allocation. The design of the exercise therapy was elaborated by physiotherapists with expertise in the treatment of PD and took into account the core areas of motor impairment in PD, such as the inability to initiate movement, difficulties with balance and gait control, falls, and deficits in the pacing of rhythmic movements. The patients did not receive any other physical therapy intervention during the course of the study.

tDCS

All of the patients received 2 weeks of tDCS stimulation (either AtDCS or PtDCS) over the dorsolateral

TABLE 2. Neuropsychological scores obtained by the sample grouped according to randomized treatment procedure [mean (SD)]

	AtDCS plus physical therapy (n = 10)			PtDCS plus physical therapy (n = 10)			*P* value			
	Baseline	Posttreatment	3-month follow-up	Baseline	Posttreatment	3-month follow-up	Group	Time	Time × group	Cut-off
Clinical scales										
UPDRS-III	27.8 (13.9)	25.4 (11.1)	25.5 (10.0)	27.6 (8.9)	23.8 (13.2)	22.4 (10.5)	.768	.100	.323	–
Hoehn-Yahr Stage	2.2 (0.6)	2.2 (0.5)	2.2 (0.5)	2.3 (0.4)	2.3 (0.4)	2.2 (0.4)	.592	.106	.625	–
Beck Depression Inventory-II	13.00 (6.1)	**10.2 (5.0)**[a]	**9.6 (9.1)**[a]	10.3 (6.6)	**7.7 (7.1)**[a]	**7.2 (5.2)**[a]	.485	**.002**	.657	<14
PDQ-39	26.1 (14.4)	21.7 (11.5)	19.8 (10.5)	25.4 (15.6)	16.8 (12.3)	19.4 (13.0)	.443	.063	.508	–
RBDSQ	6.1 (3.0)	5.4 (2.8)	5.1 (2.7)	6.2 (3.4)	5.6 (2.9)	5.4 (3.5)	.946	.326	.799	<5
Screening for dementia										
Mini Mental State Examination, maximum: 30	28.5 (1.3)	28.5 (1.4)	28.1 (1.3)	27.7 (1.4)	28.1 (1.7)	28.7 (1.2)	.716	.570	.053	>24
Global cognitive abilities										
Parkinson's Disease Cognitive Rating Scale (PD-CRS)										
;PD-CRS total score, maximum: 134	76.3 (19.6)	**82.0 (19.6)**[a]	**83.7 (18.6)**[a]	77.9 (13.1)	77.4 (13.3)	79.8 (10.0)	.922	**<.001**	**.041**	>81
PD-CRS cortical score, maximum: 30	25.3 (3.3)	25.8 (3.3)	26.4 (3.1)	26.6 (2.4)	27.2 (1.9)	26.8 (1.8)	.352	.200	.398	–
PD-CRS frontal-subcortical score, maximum: 104	51.0 (16.8)	**56.2 (17.0)**[a]	**57.3 (15.8)**[a]	51.3 (11.3)	50.2 (12.2)	53.0 (9.0)	.770	**.001**	**.025**	–
Memory										
Digit span	5.8 (0.9)	5.9 (1.0)	5.9 (0.9)	5.4 (0.9)	5.6 (0.8)	5.8 (0.6)	.526	.369	.625	>3.5
Cantab Paired Associated Learning (PAL)										
PAL, total errors adjusted	66.2 (30.8)	59.3 (36.0)	67.0 (41.3)	99.8 (23.0)	84.8 (29.7)	87.9 (35.2)	.075	.090	.767	–
PAL, total errors six shapes	15.6 (8.5)	15.7 (10.3)	18.9 (11.3)	27.0 (5.3)	20.1 (10.1)	23.8 (8.8)	.111	.094	.412	–
Attention and working memory										
Trial Making Test A, seconds	55.4 (34.2)	58.3 (38.7)	57.4 (19.6)	61.8 (29.4)	54.8 (18.0)	49.4 (16.8)	.717	.400	.562	<94
Trial Making Test B, seconds	159.14 (93.6)	130.13 (54.5)	152.63 (71.8)	182.11 (85.5)	183.78 (108.6)	181.00 (82.8)	.456	**.045**	.094	<283
Trial Making Test-B-A, seconds	121.43 (90.1)	88.75 (39.0)	112.88 (62.2)	122.67 (66.3)	130.56 (108.8)	135.00 (74.3)	.667	.084	.308	<187
Executive function										
Frontal Assessment Battery, maximum: 18	15.1 (3.6)	15.1 (3.1)	15.8 (3.1)	15.6 (1.5)	15.5 (1.9)	15.4 (2.2)	.688	.900	.698	>13.4
Semantic fluency	33.7 (11.1)	**38.7 (12.0)**[a]	**38.7 (12.7)**[a]	37.2 (11.9)	36.4 (11.0)	38.6 (10.6)	.863	**.016**	**.042**	>24
Psychomotor speed										
Cantab Reaction Time Index (RTI)										
RTI-Movement Time, milliseconds	449.6 (116.5)	465.5 (171.8)	462.8 (171.4)	502.0 (131.9)	469.3 (125.6)	501.2 (90.0)	.490	.716	.599	–
RTI-Reaction Time milliseconds	395.6 (57.7)	386.0 (64.4)	398.7 (58.8)	382.7 (54.0)	384.2 (55.9)	380.0 (64.4)	.655	.852	.573	–
Motor function evaluation										
Time Up and Go, seconds	9.23 (2.0)	9.14 (1.4)	**8.26 (1.7)**[a]	10.91 (2.0)	10.80 (1.9)	**9.59 (2.2)**[a]	.064	**<.001**	.892	–
Four Square Step Test, seconds	9.55 (1.9)	**8.29 (1.7)**[a]	**8.82 (1.7)**[a]	10.38 (1.7)	**8.94 (1.5)**[a]	**9.26 (2.4)**[a]	.365	**.005**	.804	–
Standing Stork Test, seconds	16.28 (21.5)	**22.51 (24.9)**[a]	**16.18 (22.1)**[a]	9.33 (13.4)	**14.66 (13.1)**[a]	**11.20 (7.6)**[a]	.551	**.017**	.882	–
Sit and Reach Test, centimeters	−2.0(8.7)	**+0.5 (7.6)**[a]	−2.3 (8.0)	−10.2 (6.5)	**−7.8 (6.3)**[a]	−11.7 (6.9)	**.020**	**.008**	.504	–

UPDRS-III, Unified Parkinson disease rating scale; PDQ-39, Parkinson's Disease Quality of Life Questionnaire-39; RBDSQ, Rem Sleep Behaviour Disorders Screening Questionnaire. Cut-off scores according to Italian normative data are reported. Raw scores are reported. Standard deviations in parentheses. Bold font indicates significant effects when compared with baseline.
[a]Significant when compared with baseline.

prefrontal cortex (DLPFC) contralateral to the most affected body side. Each week of tDCS treatment consisted of 5 sessions 25 minutes/day starting at the beginning of physical therapy. The stimulation was delivered by a battery-driven, constant current stimulator (BrainStim, EMS, Bologna, Italy) through a pair

of saline-soaked sponge electrodes (7 cm × 5 cm). The active electrode was placed on the left or right DLPFC, 8 cm frontally and 6 cm laterally with respect to the scalp vertex (at about halfway between F3/4 or F7/8, respectively, in the 10/20 EEG system). The reference electrode was fixed on the contralateral supraorbital area. A constant current of 2 mA was applied for 25 minutes (with a ramping period of 10 seconds at the beginning and end of the stimulation) and lasted for the entire physical therapy session. The current density (0.06 mA/cm2) was maintained below safety limits.[40] In the sham stimulation, the tDCS montage was the same, but the current was turned off 10 seconds after the beginning of the stimulation and turned on for the last 10 seconds of the stimulation period to make this condition indistinguishable from the experimental stimulation. To detect differences in the perception of the stimulation, we asked the patients to complete a questionnaire about the sensations experienced during tDCS.[50]

Statistical Analysis

Statistical analyses were performed using Statistica software (version 10; Dell Software, Tulsa, Oklahoma, www.statsoft.com).

Demographic and clinical characteristics were compared between the 2 experimental groups at baseline using Mann–Whitney *U* test for continuous variables and chi-square test for categorical variables.

Based on a review of the literature (see Supplemental Table 1) showing that repeated sessions of AtDCS improved the performance of different clinical, neuropsychological, and motor tasks, a series of analysis of variance (ANOVA) models were carried out on the same type of variables (as dependent ones) to evaluate and confirm the efficacy of AtDCS plus physical therapy. In particular, ANOVA models for repeated measures were performed with the dichotomous group variable (AtDCS plus physical therapy vs. PtDCS plus physical therapy) as between factor and time (baseline, 2-week, and 3-month follow-up) as within factor. It is worth noting that our aim was not to consider the treatment effective as a consequence of a significant difference between the 2 groups in at least 1 variable among the clinical, neuropsychological, and motor tasks (in that case the tests should have been considered simultaneous and multiple comparison adjustments would be required[51]). Rather, we aimed to evaluate if each of the target variables differed between groups and across time through a series of independent experiments, each of them referring to a specific variable and domain under study.[52]

Time measurement variables that failed to meet the assumption of normality were log-transformed before being analyzed as dependent variables with the ANOVA models. Post hoc analysis via Fisher least significant difference tests was applied to evaluate pairwise comparisons among levels of ANOVA significant factors to discover which of the comparisons were responsible for rejections in the ANOVA test.

Statistical significance was set at $P < .05$.

Results

Demographic and clinical characteristics of PD patients are summarized in Table 1. The treatment groups did not differ in the demographic and clinical variables evaluated at baseline.

Regarding the questionnaire about sensations experienced during tDCS, the scores reported in the AtDCS group were comparable with the scores in the PtDCS group ($t = -0.90$, $P = .40$), suggesting that AtDCS could not be distinguished from PtDCS. Hence, there are no reasons to reject the double-blinded character of this study.

Clinical Scales

A 2 (group) × 3 (time) ANOVA was applied to compare changes in the clinical scales administered in the 2 experimental groups.

A significant main effect of time ($F_{2,36} = 7.59$, $P = .002$) was observed in BDI-II score, suggesting a reduction of depression symptoms in the overall sample. The interaction between group and time did not reach significance, indicating similar effects recorded in the 2 experimental groups. Post hoc analysis showed a significant decrease of BDI-II scores, indicating a reduction of depressive symptoms immediately after the treatment: baseline, 11.65 (standard deviation [SD] 6.5) and posttreatment, 8.95 (SD 6.3); $P = .021$. Moreover, this change was stable at the 3-month follow-up: 8.40 (SD 7.5); $P = .0005$ (see Table 2 for details). No significant changes were found in the UPDRS-III, Hoehn and Yahr Scale, PDQ-39, or RBDSQ.

Neuropsychological Assessment

ANOVA analyses with group and time as factors were applied to compare the changes induced by the treatment on the neuropsychological scores observed in the 2 experimental groups.

Significant effects were observed for the PD-CRS total and frontal-subcortical scores, whereas no effects were observed for the cortical scores ($F_{2,36} = 1.68$, $P = .20$).

Regarding PD-CRS total scores, a significant main effect of time ($F_{2,36} = 9.34$, $P = .0005$) and a significant interaction between time and group ($F_{2,36} = 3.51$, $P = .041$) were observed. Post hoc comparisons highlighted that PD-CRS total scores increased immediately after treatment only in the AtDCS group ($P = .003$), with a stable effect at the 3-month follow-

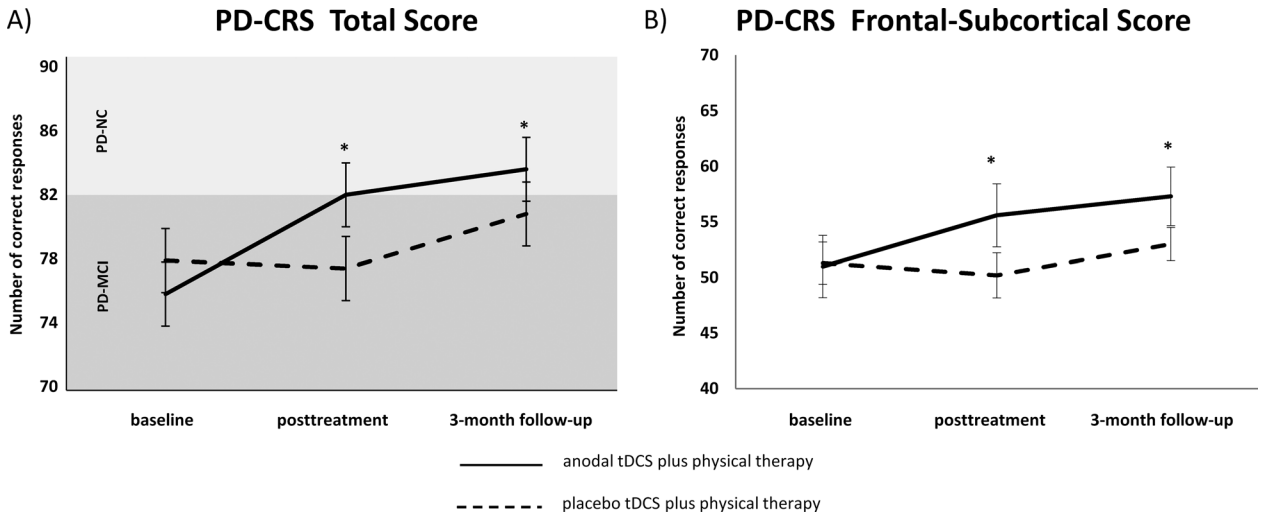


FIG. 2. Effects of the therapy protocol on neuropsychological tests. Changes in Parkinson's Disease Cognitive Rating Scale (PD-CRS) total scores (**A**) and frontal-subcortical scores (**B**) after anodal transcranial Direct Current Stimulation plus physical therapy (continuous line) or placebo transcranial Direct Current Stimulation plus physical therapy (dotted line). Error bars indicate standard error (SE) of the mean. Asterisks (*) indicate significant variations when compared with the baseline. Regarding the PD-CRS total score, on the *y*-axis the cut-off score (82) between PD mild cognitive impairment (PD-MCI) and PD normal cognition (PD-NC) is represented.

up ($P < .001$). Interestingly, following the classification according to the cut-off scores of the PD-CRS total score, the mean score obtained by the AtDCS plus physical therapy group at baseline (76.3 [SD 19.6]) was classified as PD-MCI, whereas the mean scores achieved immediately after the treatment (82.0 [SD 19.6]) and at follow-up (83.7 [SD 18.6]) were classified as normal (PD-MCI = score 65–81, PD-D = score ≤ 64, and PD-NC = score ≥ 82).[39] See Figure 2A and Table 2 for details.

Regarding the PD-CRS frontal-subcortical scores, a significant main effect of time ($F_{2,36} = 7.88$, $P = .001$) and a significant interaction between time and group ($F_{2,36} = 4.08$, $P = .025$) were observed. Post hoc comparisons highlighted that PD-CRS frontal-subcortical scores increased immediately after the treatment selectively in the AtDCS group ($P = .005$) with a stable effect at the 3-month follow-up ($P = .0002$) (Figure 2B and Table 2).

Moreover, significant effects were observed for semantic verbal fluency. A significant main effect of time ($F_{2,36} = 4.65$, $P = .016$) and a significant interaction between time and group ($F_{2,36} = 3.46$, $P = .042$) were observed. Post hoc comparison showed that the verbal fluency score increased immediately after the treatment selectively in the AtDCS group ($P = .002$), with a significant effect also at follow-up ($P = .005$) (Table 2).

Finally, significant effects were observed for the Trail Making Test part B (TMT-B). A significant main effect of time ($F_{2,36} = 3.40$, $P = .045$) and a trend of significance for the interaction between time and group ($F_{2,36} = 2.53$, $P = .09$) were observed. Post hoc comparison showed that the time necessary for completing the TMT-B decreased immediately after the treatment selectively in the AtDCS group ($P = .002$), and the effect at follow-up approached significance ($P = .070$).

No effects of the treatment were detected on other neuropsychological tests.

Motor Function Tasks

ANOVA analyses with group and time as factors were applied to compare the changes induced by the treatment on the motor function task scores achieved by the 2 experimental groups.

Regarding motor function evaluation, a significant main effect of time was observed on the Standing Stork Test ($F_{2,36} = 4.61$, $P = .017$), the Four Square Step Test ($F_{2,36} = 6.12$, $P = .005$), the Timed Up and Go Test ($F_{2,36} = 10.89$, $P = .001$), and the Sit and Reach Test ($F_{2,36} = 5.59$, $P = .008$). The interaction between group and time did not reach significance for any of the tests, indicating similar motor changes over time in the 2 experimental groups.

Post hoc analysis showed an improvement immediately after the treatment (vs. baseline) in the overall group on the Standing Stork Test (baseline: 12.81 [SD 18.2], posttreatment: 18.59 [SD 20.2]; $P = .007$), the Four Square Step Test (baseline: 9.96 [SD 1.8], posttreatment: 8.62 [SD 1.6]; $P = .002$), and the Sit and Reach Test (baseline: −6.1 [SD 8.7], posttreatment: −3.65 [SD 8.1]; $P = .026$). A persistent effect at the 3-month follow-up was shown for the Standing Stork Test (baseline: 12.81 [SD 18.2], follow-up: 13.69 [SD 16.7]; $P = .03$), and the Four Square Step Test (baseline: 9.96 [SD 1.8], follow-up: 9.04 [SD 2.1]; $P = .022$). The score obtained in the Sit and Reach Test at follow-up was not significantly different from baseline (follow-up: −7.00 [SD 8.8]; $P = .36$). See

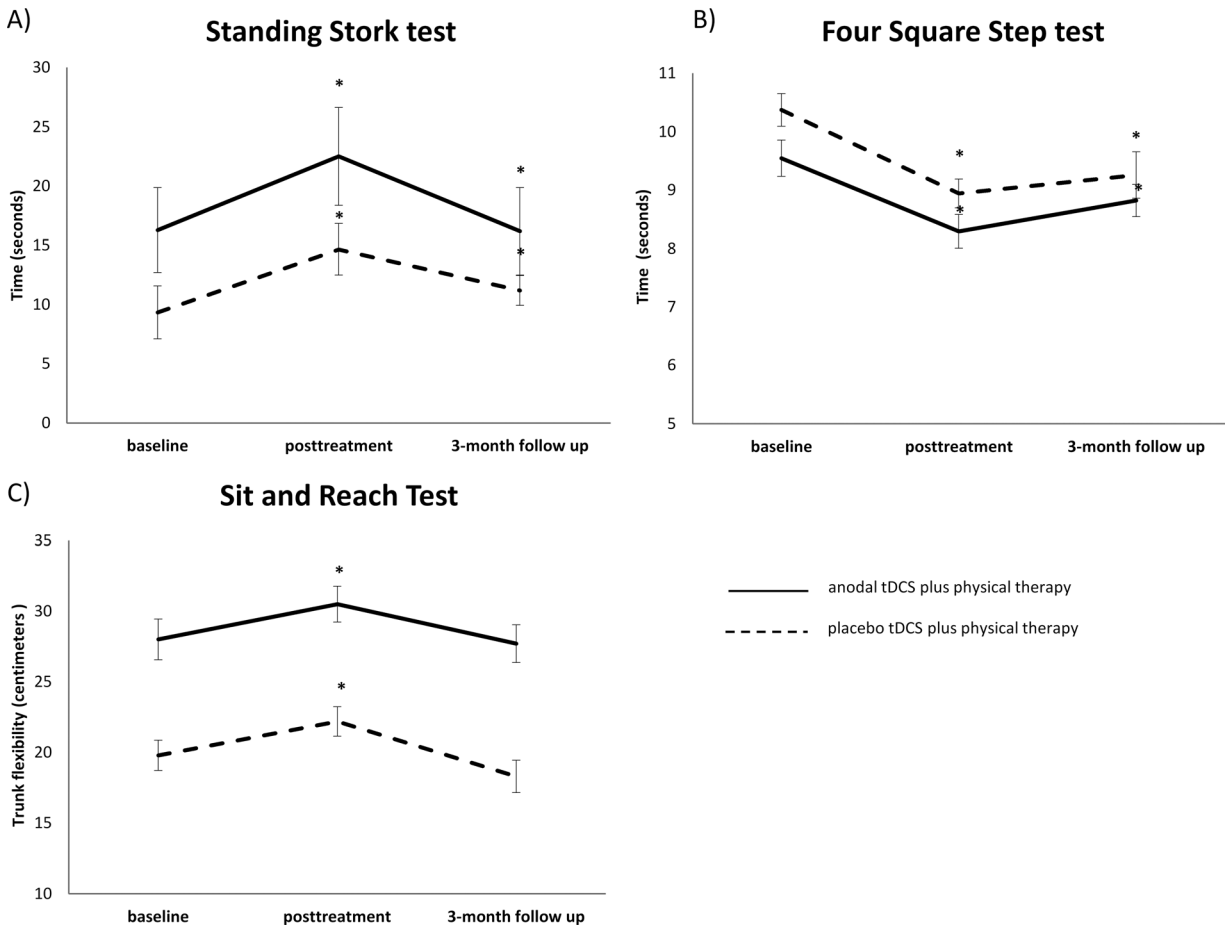


FIG. 3. Effects of the therapy protocol on motor tasks. Changes in Standing Stork Test (**A**, static balance), Four Square Step Test (**B**, dynamic balance) and Sit and Reach Test (**C**, trunk flexibility) after anodal transcranial Direct Current Stimulation (tDCS) plus physical therapy (continuous line) or placebo tDCS plus physical therapy (dotted line). Error bars indicate standard error (SE) of the mean. Asterisks (*) indicate significant variations when compared with the baseline.

Figure 3 and Table 2 for details. The Timed Up and Go Test score showed no significant changes immediately after the end of the treatment (baseline: 10.07 [SD 2.2], posttreatment: 9.97 [SD 1.9]; $P = .894$), whereas the time necessary to complete the task was significantly reduced at follow-up (follow-up: 8.92 [SD 2.1]; $P = .0002$).

In summary, all patients, independently of experimental group, showed an improvement in static and dynamic balance immediately after the 2 weeks of treatment, with persistence for up to 3 months. Furthermore, all patients achieved an increased trunk flexibility after the end of the treatment without a stability of the effect at the follow-up visit.

Discussion

PD is a neurodegenerative disorder characterized by several motor and cognitive manifestations for which effective, disease-modifying treatments remain elusive.[7]

Significant cognitive impairment is common in PD, affecting up to 25% of newly diagnosed patients.[53,54] A wide range of cognitive functions are affected, particularly executive functions, visuospatial processing, memory, attention, and language.[54] The main purpose of this study was to investigate whether the application of AtDCS applied to the DLPFC plus physical therapy for 25 minutes a day, 5 days a week, for 2 weeks would lead to significant cognitive and motor improvements in patients with PD. Specifically, we hypothesized that AtDCS plus physical therapy may lead to an improvement in cognitive functions, that is, frontal abilities and/or global cognitive abilities scales, when compared with placebo tDCS plus physical therapy. To address this question, we compared the effects of anodal or placebo tDCS plus physical therapy on patient performance in cognitive and motor tasks. Moreover, we investigated if AtDCS plus physical therapy could induce an additional improvement in motor task performance when compared with PtDCS plus physical therapy. Another important aim of the present study was to verify whether the cognitive and motor benefits recorded immediately after the treatment would persist 3 months after treatment.

Overall, the results of our study show a significant effect of AtDCS plus physical therapy on cognitive performances (PD-CRS frontal-subcortical scale, PD-CRS total scale, and verbal fluency). Interestingly, PD classified with MCI, according to PD-CRS well-established cut-offs, obtained a normal score on the PD-CRS scale following AtDCS plus physical therapy. A previous study on a Spanish PD population reported that a range of change from 10 to 13 points on the PD-CRS total score was indicative of a clinically significant change in the overall group of PD, whereas a mean of 6.00 ± 4.33 points was suggestive of minimal improvement in the PD-MCI subgroup.[55] In our sample of PD-MCI patients, an improvement of 5.7 points on the PD-CRS total score immediately after treatment and 7.4 points at 3-month follow-up was observed. Although these findings are below the clinically significant change in the overall PD population, values are in line with a minimal improvement in the PD-MCI subgroup. Moreover, only the AtDCS plus physical therapy treatment induced an improvement on the PD-CRS total score when compared with baseline, whereas the PtDCS plus physical therapy group showed no significant differences between baseline, 2 weeks posttreatment, and 3-month follow-up.

A few investigations suggest that tDCS can exert positive effects on cognitive performance in PD[27,31,34] (see Supplemental Table 1 for a comprehensive review). Another important result of our study was the absence of any tDCS effect on visual memory tasks and other cognitive abilities suggesting that a learning effect cannot explain the improvements. Hence, the facilitation effect of AtDCS over DLPFC plus physical therapy in PD patients appears to be specific to the frontal-subcortical PD-CRS score and to the semantic fluency performance rather than reflecting a general, nonspecific effect on cognitive processing. Moreover, the cognitive improvement obtained after the treatment seems to be independent from physical therapy because both groups received the same physical therapy. In addition, these results show that all PD patients reported a significant improvement on the depression scale. The similar effect shown in both groups could suggest the occurrence of a placebo effect as reported in previous studies.[35] Otherwise, because both groups received physical therapy, this finding could be in agreement with the literature on healthy individuals and patients with neurodegenerative disorders, which suggests a beneficial effect of exercise on mood.[19]

Regarding the long-term effects, we identified that the improvement obtained in the frontal-subcortical PD-CRS score and in the semantic fluency performance was stable 3 months after the end of the tDCS intervention. The possibility of inducing long-lasting beneficial effects on cognition in PD-MCI patients represents a promising result that needs further investigation.

Moreover, in contrast with previous studies that applied tDCS in PD, in the present work we failed to observe a significant additional effect of AtDCS on motor performance. Both groups had similar improvements in motor performance. This finding appears in accordance with the studies that strongly support the beneficial effects of physical exercise on neuroplasticity.[12,14,15,17,19,37] Exercise has been shown to affect a number of different neurotransmitters that could potentially contribute to the exercise-related benefits observed in PD.[18,37] Combined treatment (AtDCS plus physical therapy) did not ameliorate motor performance more than motor treatment alone (PtDCS plus physical therapy).

We might not have identified an additional effect of AtDCS on motor performance, when compared with previous studies, for methodological reasons. In the present study, we used a tDCS approach in which patients received daily tDCS treatment plus physical therapy, whereas in previous studies a single session or repeated sessions of tDCS alone were applied. Moreover, the majority of previous studies reported an enhancement in motor performance following AtDCS over the primary motor cortex (M1). Conversely, in the present report, we applied tDCS over the DLPFC during physical therapy and, therefore, this paradigm could be responsible for the lack of an additional improvement on motor functions.

The mechanisms underlying the effects of tDCS are not yet understood but may involve changes in the neuromodulation of different neurotransmitters.[24]

At the neuronal level, tDCS generates a polarity-dependent shift of resting membrane potentials and AtDCS generally enhances cortical activity and excitability, with aftereffects lasting up to 1 hour. Moreover, tDCS modifies the synaptic microenvironment by changing synaptic strength dependent on NMDA receptors or by altering GABAergic activity. It also interferes with brain excitability through the modulation of intracortical and corticospinal neurons, and it leads to transient changes in the density of protein channels localized below the stimulating electrode.[24,26] Interestingly, previous studies have demonstrated that neurotransmitters, especially dopamine, induce a nonlinear, dosage-dependent effect on the plasticity induced by tDCS because these effects depend on the relationship between current strength and the responsiveness of neurotransmitter receptors.[24,56,57]

The present preliminary results hold considerable promise not only for advancing our understanding of brain plasticity mechanisms but also for designing new rehabilitative strategies in patients with PD.

Several limitations to this pilot study need to be acknowledged, including the relatively small number

of patients and the lack of a placebo stimulation group without any treatment. A longer follow-up is required to evaluate the trajectories of progression and to clarify whether additional rehabilitative protocols should be considered persistent over time.

Despite these drawbacks, the behavioral changes observed in the cognitive abilities are quite encouraging and should serve as the basis for future research. Further studies based on larger samples of patients and including placebo and control conditions should be conducted to identify the optimal parameters for a combined treatment protocol.

Additional research with the development of uniform protocols is necessary to identify which patients at risk of developing dementia could be the optimal responders to a combined treatment protocol. ●

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.