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Noninvasive Cortical Stimulation With Transcranial Direct Current Stimulation in Parkinson's Disease

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Abstract: Electrical stimulation of deep brain structures, such as globus pallidus and subthalamic nucleus, is widely accepted as a therapeutic tool for patients with Parkinson's disease (PD). Cortical stimulation either with epidural implanted electrodes or repetitive transcranial magnetic stimulation can be associated with motor function enhancement in PD. We aimed to study the effects of another noninvasive technique of cortical brain stimulation, transcranial direct current stimulation (tDCS), on motor function and motor-evoked potential (MEP) characteristics of PD patients. We tested tDCS using different electrode montages [anodal stimulation of primary motor cortex (M1), cathodal stimulation of M1, anodal stimulation of dorsolateral prefrontal cortex (DLPFC), and sham-stimulation] and evaluated the effects on motor function—as indexed by Unified Parkinson's Disease Rating Scale (UPDRS), simple reaction time (sRT) and Purdue Pegboard test—and on corticospinal motor excitability (MEP characteristics). All experiments were performed in a double-blinded manner. Anodal stimulation of M1 was associated with a significant improvement of motor function compared to sham-stimulation in the UPDRS ($P < 0.001$) and sRT ($P = 0.019$). This effect was not observed for cathodal stimulation of M1 or anodal stimulation of DLPFC. Furthermore, whereas anodal stimulation of M1 significantly increased MEP amplitude and area, cathodal stimulation of M1 significantly decreased them. There was a trend toward a significant correlation between motor function improvement after M1 anodal–tDCS and MEP area increase. These results confirm and extend the notion that cortical brain stimulation might improve motor function in patients with PD.

Key words: Parkinson's disease; transcranial direct current stimulation; brain DC polarization; motor function; cortical stimulation

Therapeutic brain stimulation for motor function enhancement in Parkinson's disease (PD) is being increasingly investigated. Compared to pharmacological treatment, brain stimulation might have less adverse effects, particularly dyskinesias, motor fluctuations, and wearing-off phenomena. Indeed, functional neurosurgery can effectively improve motor function in PD patients and does not induce, but to the contrary, can reverse dyskinesias.[1] Although developments of invasive brain stimulation techniques for PD, such as deep brain stimulation (DBS), have reduced the risks of invasive neurosurgical procedures, effective noninvasive forms of brain stimulation would be desirable.

One main obstacle for the use of noninvasive brain stimulation is that penetrance is limited to cortical regions of the brain; thus, deep structures, such as basal ganglia, cannot be directly targeted. However, epidural motor cortex stimulation may be a valuable approach to

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improve symptoms in PD patients,[2,3] and a recent meta-analysis shows that despite substantial variability in the results of individual studies, noninvasive repetitive transcranial magnetic stimulation (rTMS) does have a significant effect on motor function in PD.[4]

Here we studied the effects of a different technique of cortical stimulation, transcranial direct current stimulation (tDCS), on motor function and cortical excitability in PD. In tDCS, the cerebral cortex is stimulated through a weak DC current in a noninvasive and painless manner. Several studies have shown that this technique modulates cortical excitability in the human motor[5] and visual cortex.[6] Furthermore, recent research has shown that tDCS can enhance some aspects of cognition[7–9] and promote the recovery of motor deficits in stroke patients.[10,11] DC stimulation has some advantages over rTMS as it is less expensive, provides a reliable sham-stimulation condition, may lead to longer-lasting modulatory effects of cortical function, and is easy to administer and perform.

PATIENTS AND METHODS

Subjects

We studied 17 patients (11 men and 6 women) aged 45 to 79 years (mean, 61.7 years) with idiopathic PD who fulfilled the U.K. Parkinson's Disease Brain Bank criteria.[12] Patients were excluded if they had other neuropsychiatric diseases, were being treated with deep brain stimulation, or could not be withdrawn from antiparkinsonian drugs for 12 hours. Written informed consent was obtained from all participants prior to inclusion in the study, which was approved by the local ethics committee (University of São Paulo) and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Experimental Procedures

All experiments were performed according to a double-blinded design. Different physicians applied the treatments and completed the evaluations, and neither the patients nor the evaluators knew whether active or sham-tDCS was performed.

Experiment 1a: Anodal Stimulation of Primary Motor Cortex (M1)

In this experiment, 9 patients underwent active anodal tDCS of the primary motor cortex (anodal M1) and sham-tDCS. Although the motor symptoms of Parkinson's disease are asymmetric in many cases, we decided to stimulate the left, dominant hemisphere only, rather than both or the most affected hemisphere. Other studies of cortical stimulation (with rTMS) have shown good results with unilateral stimulation; for instance, Bornke and colleagues[13] and Lefaucheur and colleagues[14] also targeted only one hemisphere (the dominant as well in Lefaucheur's study). Furthermore, the use of only one hemisphere eliminates a potential source of bias. The two sessions (active and sham) were separated by at least 48 hours to avoid carry-over effects. Furthermore, the order of the stimulation was pseudorandomized and counterbalanced across subjects; thus, 5 subjects received active tDCS first and 4 subjects sham-tDCS first (Fig. 1).

Experiment 1b: Cathodal Stimulation of Primary Motor Cortex (M1)

In this experiment, 8 patients underwent active cathodal tDCS of the primary motor cortex (cathodal M1) and sham-tDCS. Similarly to the experiment above, we stimulated the dominant hemisphere only. The two sessions (active and sham) were separated by at least 48 hours to avoid carry-over effects. Furthermore, the order of the stimulation was pseudorandomized and counterbalanced across subjects; thus, 4 subjects received active tDCS first and 4 subjects sham-tDCS first (Fig. 1).

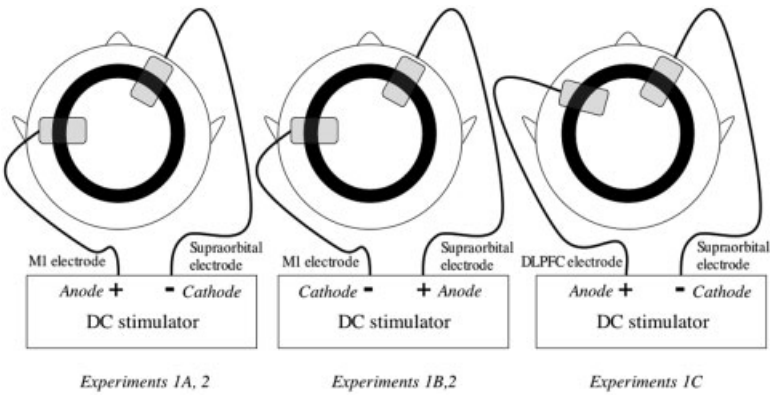

FIG. 1. Sites of stimulation and electrode montages for the different experiments.

Experiment 1c: Anodal Stimulation of Dorsolateral Prefrontal Cortex (DLPFC)

In this experiment, the 9 patients from the first experiment underwent one additional session of tDCS: anodal tDCS of DLPFC. We decided to perform this extra experiment as this would serve as a second, active control for the effects of anodal tDCS of M1. As this experiment was considered a control for the anodal M1 stimulation, we compared these results to (active and sham) anodal M1 stimulation (Fig. 1).

Experiment 2: Assessment of Motor-Evoked Potential (MEP) Characteristics After Cathodal or Anodal Stimulation of Primary Motor Cortex

We assessed the effects of primary motor cortex tDCS on MEP characteristics (amplitude and area under the curve), comparing the effects of cathodal and sham-stimulation of M1 in 8 PD patients and the effects of anodal and sham-stimulation of M1 in 9 PD patients. In both cases, the sham- and active tDCS sessions were performed with an interval of 48 hours to minimize carry-over effects.

Direct Current Stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. Patients received either anodal stimulation of left M1 or left DLPFC, or cathodal stimulation of left M1. In all cases, we compared these effects with those of sham-stimulation. For anodal stimulation of M1, the anode electrode was placed over C3 (EEG 10/20 system) and the cathode electrode over the contralateral supraorbital area. We further confirmed the intended primary motor cortex localization using single-pulse transcranial magnetic stimulation (TMS) to induce motor-evoked potentials in the first interosseous dorsalis muscle. For cathodal stimulation of M1, the position of the electrodes was reversed. To stimulate the DLPFC, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrodes placement. This method of DLPFC localization was used before in TMS studies[15] and has been confirmed as a relatively accurate method of localization by neuronavigation techniques.[16] The cathode was placed over the contralateral supraorbital area (Fig. 1). A constant current of 1 mA intensity was applied for 20 minutes. Subjects felt the current as an itching sensation at both electrodes at the beginning of the stimulation. For sham-stimulation, the electrodes were placed in the same positions as for anodal M1 stimulation; however, the stimulator was turned OFF after 5 seconds as previously described.[17] Therefore, the subjects felt the initial itching sensation, but received no current for the rest of the stimulation period.

MEP Assessment

In order to study the effects of DC stimulation on MEP characteristics, we recorded MEPs from the right first dorsal interosseous (FDI) using TMS. Focal TMS was performed using a commercially available figure-of-eight coil (outside diameter of each wing 7 cm) and a Dantec stimulator (1.5 Tesla version; Medtronic, Minneapolis, MN). Motor threshold and optimal scalp position for induction of MEPs were determined following published guidelines.[18] The coil was held tangentially to the skull with the handle pointing occipitally with an angle of 45° to the midline of the subject's head. Stimulation intensity was adjusted to achieve a baseline MEP in the FDI of about 1 mV peak-to-peak amplitude before tDCS. Stimulation intensity was kept constant for each subject throughout the experiment. The MEPs were recorded using electrodes in a belly tendon arrangement and were stored in a PC computer using the program Keypoint (Medtronic) for offline analysis. We recorded 10 MEPs for each time point (immediately before and after the treatment with tDCS) and averaged the amplitude and area under the curve.

Motor Function Evaluation

Antiparkinsonian medications (levodopa or dopaminergic agonist) were held for approximately 12 hours prior to the experiment, which was conducted at the same time of the day (morning) in all patients to avoid circadian influences.

Prior to and following all interventions, all participants underwent a battery of tests to evaluate motor function. We considered the pre-tDCS tests as baseline. Postintervention tests were performed immediately following each intervention. Our test battery included the following measures: Unified Parkinson's Disease Rating Scale (UPDRS), simple reaction time (sRT), and Purdue Pegboard test (PPT). We selected these tests as they have shown to be valid instruments to evaluate motor function in PD patients after levodopa challenge.[19] A blinded rater conducted these evaluations before and after each tDCS condition.

Motor function was initially investigated according to the motor section of UPDRS (part III). This tool allows the evaluation of tremor, bradykinesia, rigidity, postural instability, and gait and is widely employed as outcome measure in PD clinical trials.

For the simple reaction time task, patients were seated in front of a computer screen placed at eye level. A circle of 4 cm diameter was presented in the center of the screen following a warning sign (small cross in the center of the screen) after a randomly variable interval of 2 to 5 seconds. The patients were asked to push a response key as soon as they saw the circle on the screen using only the right index finger, which was rested on the key. The time between the appearance of the circle and the push of the response key was defined as sRT. The experiment consisted of blocks of 30 trials. Patients were allowed to practice for 60 trials prior to the test in order to familiarize themselves with the procedure. The stimuli were generated and response times recorded using Superlab Pro version 2.0 software (Cedrus Corp., San Pedro, CA).

The PPT consists of a wood console with a shallow dish to contain the pegs on one end of the console and 40 holes (two parallel columns of 20 holes) on the opposite end located at the middle of the console. The patients were seated directly in front of the pegboard with the shallow dish farthest away and were instructed to place as many pegs as possible in the holes with their right hand in a 30-second interval. Patients were allowed to practice for four trials prior to the test in order to familiarize them with it.

Data Analysis

Initially, we compared the baseline results for both groups of patients in order to rule out that differences between anode and cathode stimulation might have been due to a priori differences between these two groups. We then analyzed changes in motor performance (as indexed by sRT, UPDRS scores, and PPT performance) and MEP characteristics (amplitude and area). Analyses were done with Stata statistical software (version 8.0; Stata, College Station, TX). Initially, for each experiment, we calculated differences in the outcomes between post- and pretreatment scores following active and sham-intervention (anodal M1, cathodal M1, and anodal DLPFC). We performed an analysis of variance (ANOVA) to test whether there was an overall effect of the intervention (stimulation condition) on each primary outcome measure.

When appropriate, posthoc comparisons were carried out using Scheffe's correction for multiple comparisons. Furthermore, in an exploratory way, we analyzed whether the PD characteristics such as disease duration, stage of disease, motor asymmetry (more affected side), or type of PD (i.e., tremor-predominant vs. akinetic–rigid forms) were correlated to the motor changes following tDCS. We also examined whether there was a correlation between changes in motor function and changes in MEP size. We used Pearson correlation coefficient to analyze these relationships.

Furthermore, we examined whether there was a significant order effect, performing an analysis of variance and including the factor order (e.g., anodal stimulation first or sham-stimulation first).

Unless stated otherwise, all results are presented as mean and standard error of mean (SEM) and a positive change in UPDRS, sRT, or PPT indicates motor improvement. Statistical significance refers to a two-tailed P value < 0.05.

RESULTS

Table 1 summarizes demographic and clinical characteristics at baseline. The 17 patients were moderately to severely affected by PD. There were no significant differences in clinical and demographic characteristics across the different groups of patients (anodal tDCS: Experiments 1a, 1c, and 2; cathodal stimulation: Exper-

TABLE 1. *Demographic and clinical characteristics*

	All	Anodal tDCS (Experiments 1a, 1c, and 2)	Cathodal tDCS (Experiments 1b and 2)	P*
Number of subjects	17	9	8	
Male, n (%)	11 (65)	5 (56)	7 (87.5)	NS
Age, yr (SEM)	62.3 (1.6)	59.2 (3.3)	65.9 (4.6)	NS
Disease duration, yr (SEM)	12.3 (1.6)	13.7 (2.7)	10.7 (1.7)	NS
Motor UPDRS score, baseline (SEM)	37.4 (3.9)	36.9 (5.0)	38.2 (4.4)	NS
Hoehn–Yahr stage (SEM)	2.4 (0.2)	2.4 (0.2)	2.3 (0.3)	NS
Most affected side, right/left (n)	9/8	5/4	4/4	NS
Subtype of idiopathic PD (rigid–akinetic/tremor)	8/9	4/5	4/4	NS
Levodopa use, n (%)	15 (88)	8 (88)	7 (87.5)	NS
Mean levodopa use, mg (SEM)	615.0 (63.1)	681.2 (67.1)	539.2 (110.9)	NS

*Comparison between cathodal and anodal stimulation groups (student's t test for continuous variable and Fisher's exact test for categorical variables).

NS, not significant.

iments 1b and 2; Table 1). All patients tolerated the tDCS treatment well without experiencing any adverse effects, and all completed the entire experiment. Importantly, when explicitly asked, none of the patients could tell correctly whether the stimulation was active or sham.

Experiment 1a: Motor Changes Induced by Anodal Stimulation

In order to reveal the motor effects induced by tDCS, we calculated the difference between pre- and poststimulation for the sham- and active anodal M1 tDCS group and performed a one-way ANOVA to analyze whether the effects of these treatments on motor function differed (Fig. 2A). This analysis revealed a significant motor improvement after active anodal M1 stimulation compared to sham-stimulation for UPDRS ($F_{1,16} = 19.6$; $P < 0.001$; change after active tDCS = 21.9% ± 4.7%; change after sham-tDCS = −1.6% ± 2.5%) and for simple reaction time ($F_{1,16} = 6.79$; $P = 0.019$; change after active tDCS = 12.6% ± 4.1%; change after sham-tDCS = 0.6% ± 2.0%). There was no significant effect on PPT performance ($F_{1,16} = 1.62$; $P = 0.22$), although performance tended to be better after active (17.5% ± 10.0%) than after sham-stimulation (−0.1% ± 9.2%).

Experiment 1b: Motor Changes Induced by Cathodal Stimulation

Although cathodal stimulation induced a small improvement in motor function, this effect was not significantly different from sham-stimulation (Fig. 2B). We performed the same analysis as used to measure the motor effects induced by anodal tDCS and found a nonsignificant effect of cathodal M1 tDCS compared to sham-stimulation for UPDRS ($F_{1,14} = 2.5$; $P = 0.13$; change after active tDCS = 5.8% ± 1.6%; change after sham-tDCS = −2.0% ± 4.3%), simple reaction time ($F_{1,14} = 0.38$; $P = 0.54$; change after active tDCS = 5.6% ± 2.2%; change after sham-tDCS = 1.7% ± 5.5%), and PPT performance ($F_{1,14} = 3.43$; $P = 0.09$; change after active tDCS = 7.3% ± 4.6%; change after sham-tDCS = −9% ± 6.9%). It is interesting to note that the magnitude of the effects of sham-stimulation in this experiment was different from Experiment 1a; however, since in both experiments, the effects of sham-stimulation did not differ significantly from baseline values, this most probably reflects simply data variability.

Experiment 1c: Control Experiment for Anodal Stimulation (Anodal DLPFC Stimulation)

Because anodal stimulation was associated with a motor function improvement as indexed by UPDRS and simple reaction time, we tested whether this effect was specific for the anodal stimulation of M1 or whether the effects could be due to cathodal stimulation of the right frontopolar area. Therefore, we placed the cathodal electrode over the same area (right supraorbital), but placed the anodal electrode over the DLPFC. We performed the same analysis as used for Experiments 1a and 1b, but compared instead the effects of anodal DLPFC with anodal M1 and sham-stimulation (Fig. 2C). This analysis revealed a significant main effect of stimulation condition for the dependent variable UPDRS ($F_{2,24} = 8.69$;

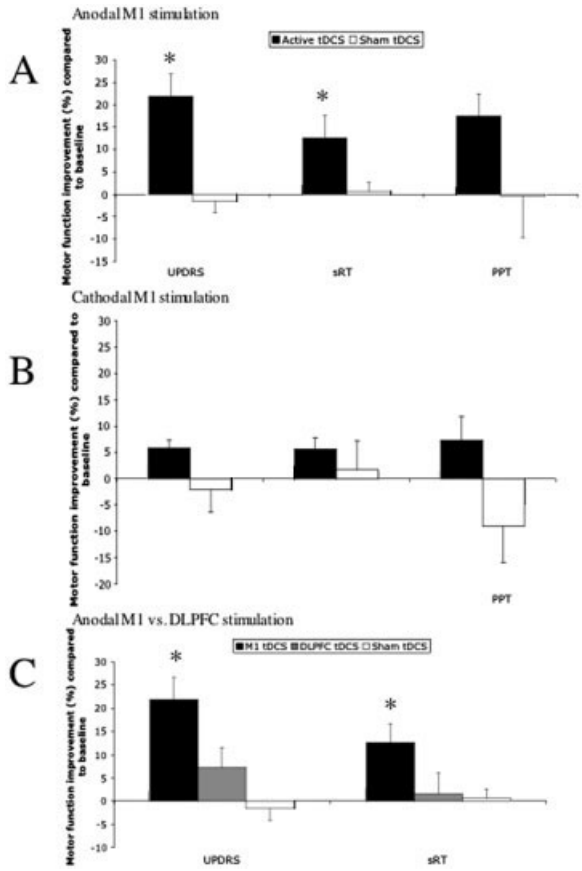

FIG. 2. Motor performance change induced by tDCS: Experiments 1a, 1b, and 1c. **A:** Mean motor function enhancement (%) compared to baseline after anodal stimulation of primary motor cortex (black column) and sham-tDCS (white column; Experiment 1a) as indexed by UPDRS, sRT, and PPT. Note that a positive change indicates motor improvement. Asterisk indicates a significant difference compared to sham-stimulation. Each column represents mean performance change ± SEM. **B:** Mean motor function enhancement (%) compared to baseline after cathodal stimulation of primary motor cortex (black column) and sham-tDCS (white column; Experiment 1b) as indexed by UPDRS, sRT, and PPT. **C:** Mean motor function enhancement (%) compared to baseline after anodal stimulation of primary motor cortex (black column), anodal stimulation of dorsolateral prefrontal cortex (DLPFC, gray column), and sham-tDCS (white column; Experiment 1c) as indexed by UPDRS, sRT, and PPT.

$P = 0.001$) and simple reaction time ($F_{2,24} = 4.06$; $P = 0.03$). As in Experiment 1a, PPT performance showed no significant effect ($F_{2,24} = 1.3$; $P = 0.29$). Posthoc tests (using Scheffe's correction) showed a significant difference in UPDRS score after anodal M1 versus anodal DLPFC stimulation ($P = 0.05$), but not between sham- and anodal DLPFC stimulation ($P = 0.30$). Similar results were obtained for posthoc comparisons for sRT: the small improvement in this test performance after anodal DLPFC was not significantly different from sham-stimulation ($P = 0.92$), but was significantly different when compared with anodal M1 stimulation ($P = 0.047$).

Experiment 2: MEP Assessment After Cathodal or Anodal tDCS of M1

We assessed the amplitude and area of MEPs induced by single-pulse TMS before and after anodal or cathodal stimulation of M1 (Fig. 3). The results of this experiment showed an increase of the MEP amplitude by 78.5% after anodal M1 stimulation. This was significantly greater than the effects found after sham-stimulation (increase of 4.7% in the MEP amplitude; $F_{1,16} = 15.45$; $P = 0.001$). Cathodal DC stimulation led to a decrease in MEP amplitude by 21.7%, significantly different from the effects of sham-stimulation (increase of 1% in the MEP amplitude; $F_{1,14} = 6.95$; $P = 0.019$). Similar results were obtained when the area under the curve was analyzed: whereas anodal stimulation significantly increased the MEP area (increase of 74.3%; $F_{1,16} = 8.1$; $P = 0.01$), cathodal tDCS significantly decreased it (decrease of 28.5%; $F_{1,14} = 8.6$; $P = 0.01$).

Correlation Between Motor Improvement and MEP Size

We tested whether MEP size was correlated with motor improvement as indexed by UPDRS and sRT after anodal M1 tDCS using Pearson's correlation analysis. There was a trend for a positive correlation between UPDRS and MEP area changes ($r = 0.62$; $P = 0.07$), but not for sRT and MEP changes ($r = 0.15$; $P = 0.7$; Fig. 4).

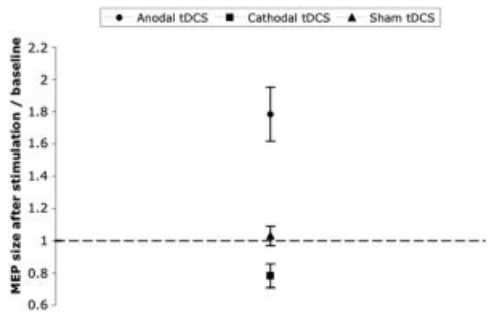

FIG. 3. Immediate effects of tDCS on the amplitude of the MEP in the right first dorsal interosseous (FDI) using transcranial magnetic stimulation to assess MEP. The ratio post- and pre-MEP was calculated for anodal primary motor cortex (M1) stimulation, cathodal M1 stimulation, and sham-stimulation. Error bars represent SEM.

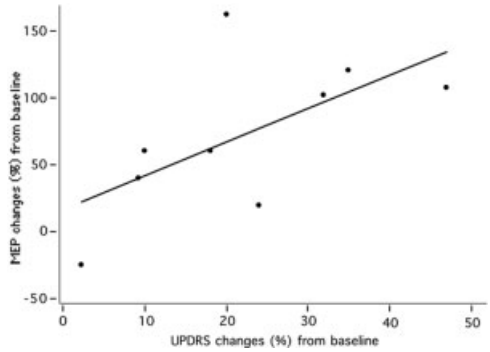

FIG. 4. Correlation between motor function improvement as indexed by UPDRS changes (*x*-axis) and motor-evoked potential area changes (*y*-axis). There was a trend toward a positive significant correlation between these two variables ($P = 0.07$). The fitted line is shown.

Correlation Between Motor Improvement and Clinical Characteristics

To test the dependency of motor improvement from clinical characteristics, we performed Pearson's correlation analyses for duration and stage of disease (indexed by Hoehn and Yahr) and two groups comparison for predominant side of motor symptoms and type of PD (akinetic–rigid vs. tremor-predominant forms). We found no correlation between duration and stage of disease and motor improvement indexed by simple reaction time ($r = -0.03$, $P = 0.92$ for duration of disease; $r = -0.35$, $P = 0.34$ for Hoehn and Yahr stage) or UPDRS ($r = 0.35$, $P = 0.34$ for duration of disease; $r = 0.53$, $P = 0.13$ for Hoehn and Yahr stage). Furthermore, there were no significant differences in the motor function improvement between patients with tremor-predominant and akinetic–rigid forms of PD ($P = 0.75$) or between patients with motor symptoms predominating on the right or left hemibodies ($P = 0.48$).

Order and Carry-Over Effect

In order to rule out carry-over effects, we compared baseline scores before each stimulation condition and showed that these values were not significantly different for the comparison anodal M1 versus sham-stimulation ($P = 0.87$ for UPDRS baseline; $P = 0.65$ for PPT baseline; $P = 0.87$ for sRT baseline). Furthermore, we examined whether our results were associated with an order effect. A one-way ANOVA with one factor and two levels (anodal M1 stimulation first, sham-stimulation first) showed that this covariate (order) was not signifi-

cant ($F_{1,16} = 0.35$, $P = 0.56$ for UPDRS evaluation; $F_{1,16} = 0.01$, $P = 0.92$ for sRT).

Finally, in an exploratory, descriptive way, as this study has not sufficient power to encompass multiple comparisons using the items of the UPDRS, we analyzed whether the motor improvement revealed by UPDRS evaluation was driven by one or more items of this scale. This analysis disclosed that rigidity had the largest scores reduction (on average two times higher than the other items;
Fig. 5).

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that anodal tDCS of M1 results in a significant motor function enhancement in PD as indexed by simple reaction time and motor scores of UPDRS and compared with sham-stimulation. Furthermore, our findings suggest that these effects are specific for tDCS polarity and site of stimulation. Although cathodal stimulation of M1 and anodal stimulation of the DLPFC also yielded a small motor function improvement, their effects were not significantly different from sham-stimulation. Finally, we show that tDCS is associated with a polarity-dependent effect on corticospinal motor excitability in PD patients: whereas anodal stimulation results in a robust increase in MEP size, cathodal stimulation slightly decreases it. These modulatory effects on corticospinal excitability seem correlated to the motor function enhancement.

This study confirms and extends the notion that the primary motor cortex might be an important target for brain stimulation in PD patients. Recent studies have shown that epidural stimulation is associated with a motor improvement in PD patients[2] and in an animal model of PD.[3] Although the results of trials investigating motor function in PD after rTMS are mixed, a recent meta-analysis showed that rTMS is associated with significant motor improvement, though the magnitude of the pooled effect size is moderate (0.62).[4] Two pathophysiological mechanisms can be proposed to explain how cortically directed stimulation may improve PD symptoms. First, cortical stimulation may induce changes throughout a distributed cortico–subcortical network that connects with and positively affects basal ganglia function. Indeed, a PET study has shown that anodal, but not cathodal, tDCS of the primary motor cortex induces an increase in the activity of the thalamic nucleus ventroposterolateral (VPL).[20] Such distant effects could be associated with specific release of neurotransmitters.[21] Second, symptoms in PD may ultimately be the consequence of the cortical dysfunction caused by the basal ganglia abnormality and stimulation of cortical sites may normalize this cortical dysfunction and thus lead to symptomatic relieve. Alternatively, the altered cortical physiology in PD may represent an attempt to compensate for the basal ganglia dysfunction and minimize clinical symptomatology, so that cortical stimulation could promote such compensatory attempts. In support of the latter hypothesis, we showed that excitability-enhancing anodal tDCS was associated with an improvement of motor function, and functional imaging and TMS studies of PD subjects have demonstrated reduced intracortical inhibition and excessive corticospinal output in basal ganglia–connected areas such as the supplementary motor area, dorsolateral prefrontal cortex, and primary motor cortex.[22–24] This suggests that the dysfunction of the basal ganglia caused by low concentration of dopamine results in a secondary and beneficial increase of cortical excitability to compensate for the underactive pallido–thalamo–cortical drive.[25–27] A further increase of cortical excitability by anodal stimulation might enhance this compensatory mechanism and thus improve motor function. Indeed, effective treatment with deep brain stimulation seems also to be associated with an increase in motor cortex excitability.[28] Consistent with this notion, we found a trend toward a positive correlation between motor function improvement and an increase in MEP size (suggesting an enhancement of cortical excitability) after tDCS.

The results of our study should be discussed in the context of rTMS studies. Lefaucheur and colleagues[14] performed a well-designed study in which they evaluated the effects of inhibitory 0.5 Hz rTMS and excitatory 10 Hz rTMS applied over the motor cortex on motor performance in PD patients and, in addition, evaluated several parameters of cortical excitability. This study

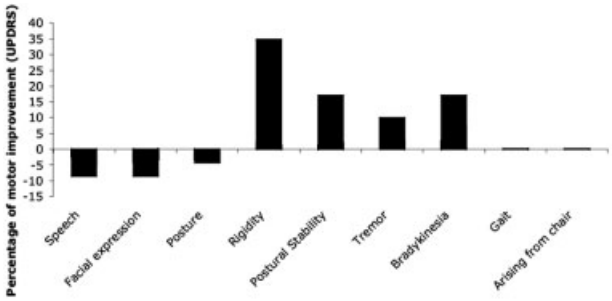

FIG. 5. Effects of tDCS treatment on the different items of UPDRS (rigidity, tremor, bradykinesia, postural instability, facial expression, speech, gait, posture, arising from chair). Note that, for some of these items, the clusters, rather than the individual items, were analyzed (e.g., tremor and rigidity). Note that the absolute mean improvement of the cluster rigidity was on average at least twice as large as the other UPDRS items/clusters.

showed that both conditions of stimulation (high- and low-frequency rTMS) lead to an improvement of motor function. These results are partially in line with our findings. Anodal tDCS of M1 induced similar behavioral effects as excitatory high-frequency rTMS of M1—also in accordance with other studies.[14,27,29,30] Cathodal tDCS of M1, however, did not result in a significant improvement of motor function, contrary to the beneficial motor effects of low-frequency rTMS of M1 seen in Lefaucheur's study.[14] Despite the fact that both techniques (tDCS and rTMS) induce similar modulatory effects in healthy subjects, the modulatory effects of these methods of brain stimulation in PD patients might be different. For instance, Lefaucheur and colleagues[14] showed that inhibitory low-frequency rTMS restores inhibitory mechanisms (increase in cortical silent period [CSP] and intracortical inhibition [ICI]) and excitatory high-frequency rTMS can affect both inhibitory (increase in CSP) and excitatory (increase in intracortical facilitation [ICF]) mechanisms; however, MEP size is not changed after both types of rTMS. Although the direction of the effects of tDCS in our study seems to be similar to Lefaucher's study—we showed that inhibitory cathodal tDCS decreased MEP size and excitatory anodal tDCS increased it—the mechanisms associated with MEP size and ICI/ICF changes are different. Whereas MEP size indexes global excitability of the corticospinal tract,[31] ICF and ICI reflect specifically the excitability of excitatory and inhibitory interneurones,[32] respectively. Therefore, the comparability of both studies in this behalf is limited. It can be derived that tDCS does modify global corticospinal excitability polarity-dependently in PD patients, as measured by MEP size, while rTMS does not. For intracortical mechanisms, it might be that tDCS has a similar effect as rTMS, since anodal tDCS enhanced intracortical facilitation and reduced inhibition, while cathodal stimulation resulted in reversed effects in healthy subjects.[33] However, it is possible that these effects differ in PD patients, similar to what has been observed in rTMS research.[24] This topic should be clarified in future studies to a greater extent.

An alternative explanation for our results could be that not only anodal tDCS of M1, but the simultaneous frontopolar cathodal stimulation (reference electrode) improved symptoms and motor performance of the patients. Nevertheless, this seems unlikely as we found that anodal stimulation of the DLPFC, which encompasses the identical reference electrode position (cathode placed over the contralateral orbit), was not associated with motor function improvement.

Ultimately, the mechanisms of action of tDCS are still not sufficiently clarified. Several different mechanisms, such as modulation of NMDA receptors with resulting changes in intracortical excitability,[34] hyperpolarization or depolarization of neuronal membranes depending on current orientation, and shifts in ionic concentrations (for review, see Nitsche and colleagues[35]), have been proposed. Regardless, it is unclear how applicable these postulated mechanisms based on testing of healthy humans might be for PD patients, given the abnormal PD brain physiology. For example, although the demonstrated effects of tDCS on corticospinal excitability are generally similar in PD as compared to the past research in healthy subjects, i.e., anodal tDCS increases it and cathodal decreases it,[5,36] the magnitude of these effects seems to differ. We found anodal stimulation to have a three times larger effect size than cathodal stimulation, while in healthy subjects the magnitude of these effects is similar.[35] Patients with PD have a baseline increase in cortical excitability attributed to the decreased input from basal ganglia.[24] This increased excitability could interfere with the inhibitory effects of cathodal stimulation.

One interesting finding of this study is the small improvement (although not significant) in motor function obtained after anodal tDCS of dorsolateral prefrontal cortex. One possibility to explain this potential effect is the nonfocality effect of tDCS; this technique employs large stimulating electrodes (35 cm^2 in our study) that induce a widespread effect in brain activity (see Lang and colleagues[20]), in contrast to rTMS that induces a more focal effect if a figure-of-eight coil is used (see Hallett[37]). However, it was shown in another study that moving the stimulating electrode 3 cm forward relative to the primary motor cortex eliminates the effects of tDCS on sequential motor learning. Thus, the functional focality of tDCS seems to be fairly restricted to the area under the electrode. Another potential explanation is a local activity change in the prefrontal cortex that can result in remote activity changes through different neural networks. For instance, it has been shown that excitatory high-frequency rTMS of the prefrontal cortex induces a release of dopamine in the caudate nucleus[21] and a small motor function improvement.[38]

Some methodological issues should be discussed. First, one of the drawbacks of a crossover design is the possibility of a carry-over effect. However, we did not expect, based on previous studies, that the effect of a single session of tDCS would last longer than 2 hours. Studies in healthy controls showed that 13 minutes of motor cortex tDCS modifies the amplitude of MEPs for the subsequent 90 minutes.[5] Furthermore, we showed that baseline evaluations before each different stimulation condition were not significantly different. Finally,

we counterbalanced the order of stimulation and separated each stimulation condition by at least 48 hours. Second, although we found a significant effect in the reaction time and UPDRS scores after anodal tDCS of M1, there was only a statistical trend toward a performance enhancement in the pegboard test evaluation. This lack of significance might result from the larger variance of results in this test. Third, we studied moderate to severe PD patients withholding antiparkinsonian medications for 12 hours. Therefore, the results of this study might not generalize to patients with milder forms of the disease. Furthermore, the effects of DC stimulation might differ with the use of levodopa and need to be studied in detail since levodopa modifies activity in the motor cortico–subcortical network and may thus significantly influence the effects of tDCS.

Despite the limitations discussed, the results of this study provide the first evidence that anodal stimulation of primary motor cortex might yield a motor benefit for PD patients and will hopefully encourage further studies evaluating the effects of tDCS on motor function in these patients. Future studies must also evaluate other parameters of stimulation, such as intensity, duration, and number of stimulation sessions. Importantly, the effects observed in this study should not be extrapolated to the clinical application of DC stimulation in PD before a proper clinical trial aiming at functional clinical benefits is conducted.

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