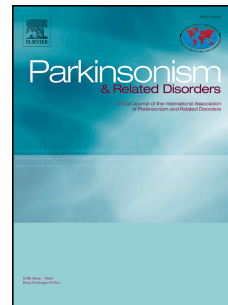


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tDCS application for postural control in Parkinson's disease: effects are associated with baseline characteristics

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Abstract

Introduction: Transcranial direct current stimulation (tDCS) improves postural response to perturbation in patients with Parkinson's disease (PwPD). However, the influence of baseline characteristics such as clinical/cognitive and postural performance on the response to tDCS remains unclear. **Objective:** To investigate whether baseline level of postural control (performance during sham condition) and clinical/cognitive characteristics are associated with tDCS-related changes in postural responses to external perturbations in PwPD. **Methods:** Twenty-four PwPD participated in this study. Clinical assessment included disease severity, disease duration, levodopa equivalent dose and global cognition. Anodal tDCS protocols targeting the primary motor cortex were applied in two separate sessions (at least 2 weeks apart): active (2 mA for 20 minutes) and sham stimulation. Seven trials with the backward translation of the support base (20 cm/s and 5 cm) were performed after tDCS. Postural outcomes included the recovery time to stable position and onset latency of the medial gastrocnemius (MG). Pearson and Spearman correlation tests were performed. **Results:** No significant correlations were observed between clinical/cognitive characteristics and tDCS-related changes in postural responses. Negative associations were observed between the baseline level of postural control and tDCS-related changes in postural responses for the recovery time ($r=-0.657$; $p<0.001$) and the MG onset latency ($r_s=-0.539$; $p=0.007$). PwPD with worse baseline postural control demonstrated greater improvement after active stimulation. **Conclusions:** Findings suggest that tDCS-related effects on postural response to perturbation are related to the baseline level of postural control, but not to clinical characteristics in PwPD. Those with worse baseline postural control responded better to tDCS.

Keywords: Postural balance; Neurodegenerative disease; Movement disorders; non-invasive brain stimulation; Electromyography; Center of pressure.

1. Introduction

Deficits in postural responses to external perturbation are common in patients with Parkinson's disease (PD) [1] and postural control impairments are associated with the increased risk of fall in this population [2,3]. Patients with PD demonstrate impaired muscle activation to respond to external perturbation, greater displacement of the center of pressure (CoP), and take longer to recover balance [1]. As pharmacological treatment has minor effects on postural responses to perturbation [1], there is a need for the development of complementary interventional approaches, such as transcranial direct current stimulation (tDCS).

tDCS is a non-invasive brain stimulation technique that applies electrical current with low intensity (1-2 mA) across the scalp to modulate the excitability of cortical and subcortical areas. Of particular interest to PD, anodal tDCS has been shown to increase cortical excitability [4] and levels of extracellular dopamine in the striatum [5]. Recently, we demonstrated that a single session of anodal tDCS over the primary motor cortex (M1) with 2 mA decreased the time to recover the stable position (recovery time) and onset latency of medial head of gastrocnemius (MG) after external perturbation in patients with PD [6]. These tDCS-related improvements may be due to enhanced sensorimotor integration and involvement of the automatic pathway for postural control [6].

Although tDCS seems to be a promising complementary therapy in PD, studies applying tDCS for postural control improvement in patients with PD often report variable responses, with some patients not benefiting from tDCS [4,6–8]. Existing studies have not identified predictors of response to tDCS in PD [6–8]. This lack of knowledge limits a more tailored approach, which is needed for optimal clinical use of tDCS. In healthy population, individual characteristics, such as the baseline level of motor function, have been shown to influence the effects of tDCS [9,10]. Thus, the identification of factors that

may influence the responsiveness to tDCS in PD is needed and may contribute to the development of optimized protocols for postural control. In this study, we extend our previous findings [6] by investigating whether baseline level of postural control and clinical/cognitive characteristics are associated with tDCS-related changes in postural responses to external perturbations in patients with PD. We hypothesized that patients with PD with worse baseline level of postural control (e.g. longer recovery time and MG onset latency recorded in the sham condition) would benefit more from tDCS due to possible greater room for improvement [9,10]. Additionally, based on findings reported by Fregni and colleagues [4], we expected to observe no significant association between the response to tDCS and clinical/cognitive characteristics.

2. Materials and Methods

2.1 Participants

Twenty-four patients with PD participated in the study. Exclusion criteria were: Hoehn & Yahr stage > III; the presence of any uncontrolled disease that could affect peripheral sensory function (e.g. diabetes); musculoskeletal, vestibular, or visual impairments that could affect balance; risk of receiving tDCS (e.g. neural implants, pacemaker, history of seizures and epilepsy); and PD medication-changes during the study period [6]. This study was approved by the research ethics committee from São Paulo State University (CAAE: 87653818.2.0000.5465) and participants gave written consent before participation in the experimental procedures.

2.2 Procedures

Patients with PD completed three visits to the laboratory. Visit 1 involved the clinical/cognitive assessments through the motor section of the Movement Disorders Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS III), levodopa

equivalent daily dose, and the Mini-Mental State Examination. Visits 2 and 3 (at least 2 weeks apart) involved the stimulation protocol and postural assessment.

Participants remained seated on a chair during the stimulation protocol and two tDCS conditions were applied using the Microestim GENIUS (NKL Electronic Products): active and sham. For the active condition, the stimulation with 2 mA was applied for 20 minutes. For the sham condition, the stimulation was applied for 10 seconds. In both tDCS conditions, current was ramped-up at the beginning and ramped-down at the end of the stimulation for 30 seconds. The order of the conditions was randomized and counterbalanced across the sample. Anodal electrode was positioned over the M1 of the most affected cerebral hemisphere (C3/C4 on the 10-20 international electroencephalogram system) and the reference electrode (both 35 cm²) was positioned over the contralateral supraorbital region for both stimulation conditions [11]. The most affected side was determined through the MDS-UPDRS items [11]. Immediately after the tDCS protocol, participants performed seven trials with temporally unpredictable external perturbation applied by the backward translation of the support base (20 cm/s and 5 cm) [6]. The backward translation of the support base induces a forward body sway [6,12]. Understanding postural responses in this situation is important because most falls in PD occur in the forward direction [13]. For security, participants used a harness system during all postural assessments. The stimulation protocol and assessments were performed during the “ON” state of PD medication (approximately 1 hour after medication intake).

We selected the MG onset latency of the most affected limb and recovery time as outcome variables in the current study because only these two outcome measures (among many others EMG and CoP measures assessed) responded significantly to tDCS in our previous study [6]. To acquire the electromyography, we used a Trigno™ Wireless System (Delsys, Inc. - 2000 Hz) with the sensor positioned over the MG muscle of the

most affected limb. Also, a force plate (AccuGait, Advanced Mechanical Technologies, Boston, MA – 200 Hz), positioned on the perturbation equipment was used to assess the recovery time to the stable position. The perturbation, the electromyography, and the CoP activity were synchronized through one active marker of the optoelectronic capture system (Optotrack - NDI® - 200 Hz) and an accelerometer (Trigno™ Wireless System – Delsys - 148.15 Hz) positioned in the force plate [6]. Further details about experimental procedures, signal processing, and outcome parameters can be found in our previous study [6]. A brief illustration is provided in the supplemental material (Figure S1).

2.3 Statistical analysis

The MG onset latency and recovery time were calculated as the mean of the seven trials with postural perturbation for each stimulation condition. The tDCS-related changes in the outcome measures were calculated as the difference between the two sessions (i.e., $\Delta = \text{active} - \text{sham}$). Pearson and Spearman correlation tests were performed, according to data distribution, to analyze the association of tDCS-related change in the outcome measures with clinical/cognitive characteristics and the baseline level of postural control (defined as the value of the postural control parameters recorded in the sham condition).

3. Results

Table 1 shows the participants' demographics, clinical and cognitive characteristics, the baseline level of postural control, and the tDCS-related changes in postural responses to external perturbations.

3.1 Baseline level of postural control and tDCS-related changes in postural responses

Significant moderate negative associations (improvement) were observed between the baseline level of postural control and tDCS-related changes in postural responses to external perturbation: recovery time ($r = -0.657$; $p < 0.001$) (Figure 1a) and MG onset latency ($r_s = -0.539$; $p = 0.007$) (Figure 1b).

3.2 Clinical/cognitive characteristics and tDCS-related changes in postural responses

No significant correlations were observed between patients' clinical/cognitive characteristics and tDCS-related changes in postural responses to external perturbation (Table 1).

INSERT TABLE 1

INSERT FIGURE 1

4. Discussion

The current study investigated whether the baseline level of postural control and patients' clinical/cognitive characteristics are associated with tDCS-related changes in postural responses to external perturbations in patients with PD. We observed that the baseline level of postural control, but not clinical/cognitive characteristics, was moderately associated with tDCS-related changes in postural responses. Those patients with worse baseline postural control (longer recovery time and MG onset latency) demonstrated greater improvement in postural response to external perturbation after anodal tDCS, likely due to a greater room for improvement [9,10]. Our findings are in line with previous studies reporting that participants with worse motor performance at baseline demonstrated greater improvement after tDCS [9,10]. Thus, although further

research is needed for the development of more specific guidelines, the level of deficits in postural control at baseline seems to be an important factor in identifying which patients are more likely to respond better to tDCS. Moreover, it is possible that patients with PD with better baseline postural control require different stimulation protocols (e.g. greater intensity, other montages of electrodes, multiple sessions of tDCS, and/or combination with other motor and/or cognitive interventions) to benefit from tDCS-based interventions.

Anodal tDCS may have facilitated cortical and subcortical activation to respond to the perturbation [12]. As a consequence, anodal tDCS may have improved sensorimotor integration and the so-called “automatic pathway”, which involves direct projections from M1 to the spinal cord, resulting in better postural response [12]. Delays in the onset of a postural response to perturbation can be due to slowed sensory or motor conduction and delay in central processing (for sensorimotor integration) [14]. Thus, given the observed faster response to perturbation after anodal tDCS [6], it is possible to suggest that tDCS led to faster neural conduction and/or integration of sensory inputs about the perturbation.

Baseline clinical/cognitive characteristics seem to not relate to the effects of tDCS on postural responses to perturbation in patients with PD. Our results corroborate with a previous study that indicated no correlation between motor improvement after a single session of anodal tDCS and the duration and stage of PD [4]. These results suggest that patients at different levels of clinical/cognitive characteristics may respond similarly to the tDCS [4].

Current findings should be interpreted carefully as our study included a small sample size and a limited number of parameters of postural response. The lack of EMG of the knee, hip, and trunk muscles and kinematics analysis of the ankle, knee, hip, and

trunk joints did not allow us to determine whether participants used the ankle or hip strategy in response to perturbation. Identifying the specific effects of tDCS on the ankle and hip strategies may help to fine-tune tDCS interventions designed to improve postural control. Also, our study analyzed the influence of participants' characteristics on a single session of tDCS, and interventions with multiple sessions of tDCS should be explored. Future studies are necessary to identify additional characteristics of tDCS responders which may optimize the clinical use of tDCS in patients with PD. In addition, other studies should investigate the effect of individual characteristics in different assessments/domains of postural control, such as standing posture and clinical tests of balance.

In conclusion, we have demonstrated that the baseline level of postural control, but not clinical/cognitive characteristics, is associated with tDCS-related changes in postural responses to perturbation in patients with PD. Greater improvement following tDCS was observed in those with worse baseline postural control. Current findings may contribute to the development of individualized tDCS protocols for postural control rehabilitation in patients with PD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Figure Caption

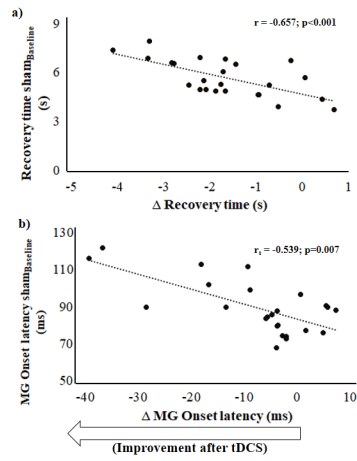
Figure 1. Significant correlation between the baseline level of postural control and tDCS-related changes in postural responses for recovery time (a) and MG onset latency (b).

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Table 1. Baseline characteristics of the sample and correlation between the clinical/cognitive characteristics and rate of changes in postural responses induced by tDCS. Parametric variables are displayed as mean \pm standard deviations and non-parametric variables (scales and non-normally distributed data) as medians (quartiles).

Variables	Mean \pm std. or Median (1 st /3 rd quartiles)	Correlation coefficient/p-value	
		Δ MG onset latency	Δ Recovery time
Clinical/Cognitive			
Sex (Male/Female)	14/10	---	---
Age (years)	68.9 \pm 8.5	0.047/0.829 [#]	0.239/0.261
Weight (Kg)	72.7 \pm 11.4	0.271/0.200 [#]	0.244/0.250
Height (cm)	164.5 \pm 10.7	0.043/0.843 [#]	0.116/0.591
LED (mg/day)	545.0 \pm 288.6	-0.195/0.360 [#]	-0.349/0.095
MDS-UPDRS III (score)	33.5 (30.0/41.5)	0.253/0.232 [#]	0.031/0.884 [#]
MMSE (score)	27.5 (26.0/28.0)	-0.157/0.462 [#]	-0.096/0.657 [#]
Disease duration (years)	3.0 (3.0/7.0)	-0.125/0.559 [#]	-0.269/0.205 [#]
EMG and CoP			
Recovery time-sham (s)	5.6 \pm 2.3	---	---
Recovery time-2 mA (s)	3.9 \pm 1.7	---	---
MG onset latency-sham (ms)	89.5 \pm 17.2	---	---
MG onset latency-2 mA (ms)	81.8 \pm 16.1	---	---
Delta (2 mA - sham)			
Δ Recovery time (s)	-1.7 \pm 1.2	---	---
Δ MG onset latency (ms)	-3.8 (-11.3/-0.6)	---	---

Note: CoP = center of pressure; EMG = electromiography; LED = Levodopa Equivalent Daily Dose; MDS-UPDRS III = motor section of Movement Disorders Society – Unified Parkinson’s disease Rating Scale; MG = medial head of gastrocnemius; MMSE = Mini-Mental State Examination; std = standard deviation; Δ = delta; # Spearman correlation test. The same 24 patients with PD and the same data of the previous study (Beretta et al., 2020)[6] were used in this secondary analysis.



Highlights

- tDCS improves postural response to perturbation in people with PD
- Postural control baseline level influence tDCS-related effects on postural response
- tDCS-related effects on postural response aren't related to clinical characteristic

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