Can transcranial direct current stimulation on the dorsolateral prefrontal cortex improve balance and functional mobility in Parkinson's disease?

Eduardo Lattari[a,b], Samara Sezana Costa[c], Carlos Campos[b,d, f], Aldair José de Oliveira[e, f], Sérgio Machado[a,b, f], Geraldo Albuquerque Maranhao Neto[c, f]

[a]*Physical Activity Neuroscience Laboratory, Physical Activity Sciences Postgraduate Program - Salgado de Oliveira University (UNIVERSO), Niterói, Brazil*

[b]*Laboratory of Panic & Respiration (LABPR), Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*

[c]*Physical Activity Sciences Postgraduate Program - Salgado de Oliveira University (UNIVERSO), Niterói, Brazil*

[d]*Polytechnic Institute of Porto, Health School, Porto, Portugal*

[e]*School of Physical Activity, Rural Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.*

[f]Intercontinental Neuroscience Research Group

Corresponding author: Prof. PhD Sergio Machado. Physical Activity Neuroscience Laboratory, Physical Activity Sciences Postgraduate Program - Salgado de Oliveira University (UNIVERSO), Niterói, Brazil. **E-mail:** secm80@gmail.com

Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique increasingly explored for Parkinson's disease (PD). Although evidence is still inconsistent, there are preliminary findings suggesting its efficacy to improve motor function in individuals with PD, as the role of secondary motor areas remains unclear. The goal of this study was to investigate the effects of left dorsolateral prefrontal cortex (DLPFC) tDCS on balance and functional mobility of individuals with PD. Seventeen individuals with PD, on-medication, aged between 40 and 90 years were recruited to enroll in a double-blind, randomized, cross-over trial. Each participant completed two conditions at least 48 hours apart, namely anodal-tDCS and sham-tDCS (placebo).The a-tDCS condition targeted the left DLPC (F3) and was applied during 20 minutes using a 2 mA current intensity. In the sham-tDCS condition, electrode position remained the same but the stimulator was turned off after 30 seconds. Functional mobility and balance were assessed using the Berg Balance Scale, Dynamic Gait Index and Timed Up and Go. There were significant differences between conditions on all outcome measures, as the a-tDCS condition was associated with better performance in comparison to the sham condition ($p<0.05$). Our findings suggest that a-tDCS on the left DLPFC improves balance and functional mobility in comparison to sham-tDCS. Compensatory mechanisms that support motor function in individuals with PD may have been enhanced by a-tDCS on the DLPFC, leading to improved functional mobility and balance. Future trials should explore left DLPFC stimulation with larger samples and compare t-DCS protocols targeting several brain regions.

Key-words: Parkinson's disease, transcranial direct current stimulation, non-invasive brain stimulation, balance, functional mobility

1. Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases in the world, with an annual incidence of 4.5 to 19 cases per 100,000 [1]. PD prevalence is around 0.5-1% in people aged between 65 and 69 years, increasing to 1-3% among individuals aged over 80 years [2]. PD is associated with the degeneration of dopaminergic neurons of the substantia nigra, hindering dopaminergic circuits, especially motor circuits [3, 4]. Thereby, persons with PD display several motor symptoms such as rigidity, postural instability, progressive bradykinesia, and tremor [5]. Gait impairment is also one of the major motor dysfunctions in PD, leading to high levels of disability and poor quality of life [6]. The motor symptoms experienced by patients also increase falls and reduce their functional independence [5].

Although drug therapy is the most commonly employed treatment, the options in use today only provide symptom relief and do not control or prevent disease progression [7]. Moreover, several side effects such as postural hypotension, nausea, dyskinesias, and hallucinations are also experienced by patients during drug therapy [8]. Thereby, searching for new alternative treatments is essential and non-invasive brain stimulation techniques are interesting alternatives for PD management. Two meta-analyses have reported modest therapeutic effects of high-frequency repetitive transcranial magnetic stimulation on motor symptoms of individuals with PD [9, 10]. There is less evidence regarding transcranial direct current stimulation (tDCS), but this technique has been growingly explored as a therapeutic tool for individuals with PD [11].

tDCS produces a low electric current over the selected brain areas [12], allowing to modify neuronal transmembrane potential, influence excitatory levels and modulate firing rates of isolated neuronal cells [13-15]. There are different tDCS procedures applied in research: anodal stimulation (a-tDCS), that increases cortical excitability of target brain regions; placebo stimulation (sham-tDCS), where the stimulator is turned off after a small period of stimulation; and cathodal stimulation (c-tDCS), which decreases cortical excitability of target brain regions [16].

Recently, there has been a growing interest on tDCS as a tool to reach optimal brain activity, modulate cortical excitability and optimize neuroplastic

changes, allowing to use this technique as a possible adjunct to rehabilitation. Some studies have reported significant positive results of tDCS on motor function in PD [11, 17]. However, the systematic review from Elsner et al. (2016) comparing active tDCS to sham-tDCS stated that there is no evidence supporting the effects of tDCS on gait speed of individuals with PD [18].

The incongruent findings can be likely explained by the diversity of tDCS protocols applied. For instance, stimulus intensity and duration can clearly influence the effects on balance and functional mobility [19-21] but few studies have been conducted to explore how these variables play a role on tDCS response in individuals with PD. Furthermore, the targeted brain areas are also a critical factor in tDCS response. Most tDCS studies with individuals with PD target the primary motor cortex and although there is increasing knowledge about the importance of the primary motor cortex in short- and long-term motor skill learning, little is known about the role of secondary motor areas, especially in short-term motor performance [22-25]. The prefrontal cortex also seems to play a clear role in functional mobility as there are several functional near-infrared spectroscopy studies showing that brain activity is increased in this area during walking [26, 27].

Thereby, the goal of this study was to investigate the effects of left dorsolateral prefrontal cortex (DLPFC) a-tDCS on balance and functional mobility of individuals with PD.

2. Materials and Methods

2.1. Participants

Individuals with PD were recruited from clinics located in Montes Claros (Minas Gerais, Brazil) and Rio de Janeiro (Rio de Janeiro, Brazil). To be included in the study, participants had to be on an optimal and regular medication regimen of levodopa or another antiparkinsonian drug (levodopa equivalent dose greater than or equal to 300 mg per day) and be able to walk independently. Participants were excluded if they had: cognitive impairment according to Mini-Mental State Examination (MMSE) [28]; history of epilepsy; antiparkinsonian drug regimen changes during or within three weeks before the experiment; neurological, vestibular, visual or psychiatric disorders; cerebral aneurysm; previous surgery involving metallic implant.

Before starting the trial, participants were informed about all experimental procedures and signed a written consent form. This study was also approved by the Institutional Ethics Committee of the Salgado de Oliveira University (#1.591.903). A total of 17 individuals with PD, aged between 50 and 91 years, were included in this study. Participants averaged 2.35 ± 1.06 on the Hoehn and Yahr scale as well as 18.0 ± 8.96 in the motor domain of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Participants' sociodemographic and clinical characteristics are described at Table 1.

INSERT TABLE 1 HERE

2.2. Experimental Procedure

Participants were assessed by an experienced evaluator who completed the Hoehn and Yahr staging scale and the UPDRS-III. After the initial screening, participants who met the inclusion criteria engaged in a double-blind, randomized, cross-over trial, to assess the effects of tDCS on balance and functional mobility. Thereby, each participant completed two conditions: a-tDCS and sham-tDCS (placebo). The a-tDCS condition targeted the left DLPFC and was applied during 20 minutes using a 2 mA current intensity. In the sham-tDCS condition, the participants remained 20 minutes with the electrodes placed in the same positions as the a-tDCS condition but the stimulator was turned off after 30 seconds of active stimulation. To assure that sham-tDCS had no effects on the outcome measures, a pilot cross-over study was conducted with 6 individuals with PD who completed both sham-tDCS and a control condition (20 minutes of sitting). There were no significant differences between both conditions in any of the outcomes ($p > 0.05$), allowing to use of sham-tDCS as a placebo in this trial.

Experimental conditions were carried at least 48 hours apart (one week maximum) to avoid possible carry-over effects. The order of conditions was counterbalanced and randomized across participants by a third researcher using a website for randomization procedures. In each condition, electrodes were removed in the end of each condition in order to complete assessment procedures. Outcome measures were then completed by an independent and

blind evaluator immediately after each condition. Two minutes of rest were allowed between each test.

2.3. tDCS Protocol

The participants remained comfortably seated in a chair within the laboratory. The electric current of 2 mA was applied using a pair of pads soaked in saline solution (NaCl 140 mmol dissolved in Milli-Q water) comprising the two 5x7 cm electrodes [12]. The electrodes (anode and cathode) were connected to a continuous current stimulation device with three 9V batteries with a maximum output of 10 mA. The batteries were regulated by a digital multimeter (EZA EZ 984, AU12 China) with a standard error of 1.5. For a-tDCS the anode was placed on the left DLPC, located in the electrode area F3 according to the international 10–20 EEG system [30]. The cathode was placed on the right orbitofrontal cortex (Fp2). In the sham-tDCS condition, the electrodes were placed in the same positions. However, the stimulator was turned off after 30 seconds, acting as a placebo condition. Participants usually report tingling sensations or itching from the initial electrical stimulation but there is evidence that there are no stimulation effects has the device is turned off during the remaining time [31].This procedure allows the subjects to become blinded to the type of stimulus that they will receive during the experiment [32]. Both stimulation conditions lasted 20 minutes.

2.4. Outcome Measures

All the participants were familiarized with the outcome assessment procedures at least a week before testing. The Berg Balance Scale (BBS) was used to assess functional balance by rating from 0 (worst) to 4 (best) patients' performance on 14 tasks common to daily living (e.g. seating, turning, picking up objects) [33]. The Dynamic Gait Index (DGI) version of De Castro's et al. [34] was used to evaluate functional mobility as it assesses the patients' ability to adjust gait in 8 conditions (e.g. speed change, avoiding objects). Each task was rated between 0 (severe impairment) and 3 (normal), allowing for a maximum score of 24 points, with a score of 19 points or less meaning increased risk of falling [35]. The Timed Up and Go (TUG) test was also used to assess functional mobility as it has high reliability for individuals with PD [36]. This test measures the time

needed for the participant to get up from a sitting position, walk a distance of 3 meters, return, and sit down again (less time equates to better performance).

2.5. Statistical Analysis

Means and standard deviation were used to report samples characteristics and outcome measure data. Several paired *t*-tests were completed in order to compare the outcome measures between conditions. All analysis were performed with a significance level of $p<0.05$, using the statistical pack SPSS 20.0.

3. Results

There were not any drop-outs from the trial and all 17 participants were included for analysis. Figure 1 presents the comparison between the a-tDCS and sham-tDCS conditions on all the outcome measures. There was a significant difference between conditions on BBS score (t = - 5.399; $p \leq 0.001$), with the a-tDCS condition displaying better performance (42.82 ± 12.17) in comparison to the sham-tDCS (41.06 ± 12.28). There was also a significant difference between conditions regarding DGI (t = - 5.607; $p \leq 0.001$), with the a-tDCS displaying higher scores (16.18 ± 7.48) in comparison to the sham-tDCS (13.88 ± 8.31). Finally, there were also significant differences between conditions regarding TUG test performance (t = 2.396; p = 0.029). In the a-tDCS condition participants completed the test in less time (24.35 ± 18.97) in comparison to the sham-tDCS (29.18 ± 24.17).

INSERT FIG. 1 HERE

4. Discussion

The goal of this study was to investigate the effects of a-tDCS on balance and functional mobility of individuals with PD. Our findings suggest that a-tDCS on the left DLPFC improves balance and functional mobility in comparison to sham-tDCS. Findings regarding the effects of tDCS in individuals with PD have been fairly inconsistent. A recent systematic review has reported that tDCS may reduce motor symptoms in individuals with PD, although there is no sufficient data supporting its effects on gait performance [18]. There is even evidence suggesting that tDCS does not even enhance other rehabilitation procedures in

individuals with PD. Costa-Ribeiro *et al.* [37] analyzed the effects of tDCS combined with cueing gait training on functional mobility of individuals with PD. The a-tDCS (anode placed in Cz) plus training group displayed similar improvements on several gait-related outcome measures in comparison to sham-tDCS combined with training.

In contrast, Kaski *et al.* [23] found a significant benefit of applying a-tDCS (2 mA; anode 10%–20% anterior to Cz) during tango dancing, improving trunk peak velocity during dancing. Furthermore, there were also modest improvements in functional mobility measures as well as an increase in overall gait speed and peak pitch trunk speed in comparison to sham-tDCS. Another study from this research group tested if combining tDCS in the same brain region with physical training could improve gait and balance in individuals with PD [24]. Participants performed gait and balance training while completing two stimulation conditions, namely 15 minutes of 2 mA a-tDCS in the primary motor and premotor cortex) and sham-tDCS. Although participants experienced gait speed improvements in both conditions, the effects of combined a-tDCS plus training were significantly higher. Furthermore, this study also included a group who completed stimulation procedures (a-tDCS and sham) without performing any kind of training, with the results showing that there were no isolated benefits of tDCS alone on both gait speed and balance.

Thereby, there is some evidence suggesting that combining tDCS with other intervention can maximize effects on balance and functional mobility, but the evidence supporting the effects of tDCS alone is lacking. The lack of consistent evidence of tDCS may be explained by the different stimulation areas chosen by researchers. For instance, Fregni *et al.* [38] assessed the effects of tDCS using different electrode montages and found that a-tDCS in the primary motor cortex (C3) improved motor function (simple reaction time), while a-tDCS on the dorsolateral prefrontal cortex (F3) had no effects. Benninger *et al.* [17] applied an 8 session a-tDCS protocol to individuals with PD, alternating anode position between the pre- and motor cortices (Cz) and the prefrontal cortices. The authors reported short-term improvements on gait and bradykinesia in the a-tDCS group compared to the sham-condition. However, as the authors actively stimulated two sites in the protocol, it is not possible to understand which brain region underlies the observed improvements.

It is quite clear that most studies applying tDCS to individuals with PD aim to modulate cortical excitability in the primary motor cortex and medial pre-motor cortex (supplemental motor area - SMA). SMA is impaired in individuals with PD, hindering the internal regulation of movement [25]. This can explain the negative findings reported by several authors, as tDCS may not be able to reverse disease-related underactivation in this region. However, it is important to highlight that abnormal SMA activity is actually compensated by enhanced activity in other regions [25, 37, 39]. Thereby, in our study the compensatory mechanisms that usually support motor function in individuals with PD may have been enhanced by a-tDCS on the dorsolateral prefrontal cortex, leading to improved functional mobility and balance.

There are two possible pathways that can support this hypothesis. First, there have been reports supporting the role of the prefrontal cortex in spatial orientation [40, 41]. There are also studies highlighting that the prefrontal cortex is activated while controlling locomotion in challenging walking conditions [22, 27]. Thereby, increased excitability on the dorsolateral prefrontal cortex may have enhanced visuo-spatial processing, allowing for improved balance and functional mobility. Second, lateral premotor areas may have been directly or indirectly targeted by tDCS: directly, as placing the anode in the F3 site may also target these regions which are anatomically located right next to the dorsolateral prefrontal cortex; indirectly because the dorsolateral premotor cortex is interconnected with prefrontal areas [42]. This is quite important has the lateral premotor areas are the main brain regions who compensate for SMA activity impairment [25, 38]. There is also evidence suggesting that the dorsolateral premotor cortex plays a clear role in visuo-spatial attention and movement anticipation [43], abilities that are critical to efficient balance and functional mobility.

Regardless of the positive findings, the reported trial has several limitations. The sample size lacks the power to establish conclusive results regarding the effectiveness of tDCS on the left DLPFC to improve balance and functional mobility in individuals with PD. Furthermore, it is not possible to state that the observed effects were explained by enhanced DLPFC activity has there was not an active control condition targeting a brain region that has not been related to motor performance and balance. Individuals with PD were also

assessed during the “on” medication stage and it would be interesting to understand if the results could be replicated in the “off” medication phase.

5. Conclusion

In this trial, a single session of a-tDCS applied on the left DLPFC improved balance and functional mobility in individuals with PD in comparison to sham-tDCS. Future trials should explore left DLPFC stimulation with larger samples and compare t-DCS protocols targeting several brain regions, allowing to pinpoint the gold-standard tDCS procedures to improve rehabilitation outcomes in individuals with PD. Although the literature regarding t-DCS for PD is fairly inconsistent, these are promising results and researchers should further explore this technique as it has a favorable safety profile, better tolerability, applicability and cost-effectiveness in comparison to other brain stimulation techniques.

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Figure legends

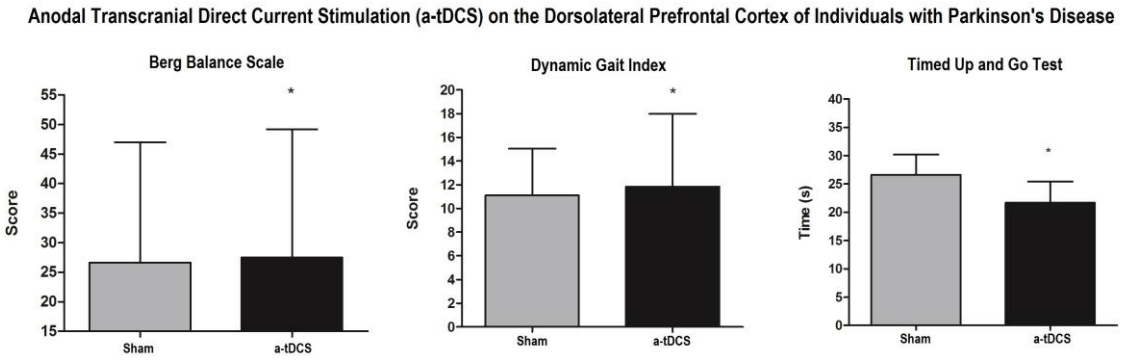

Fig. 1. Acute effects of tDCS on BBS, DGI, and TUG in Parkinson's disease.

**Significant difference between the conditions*

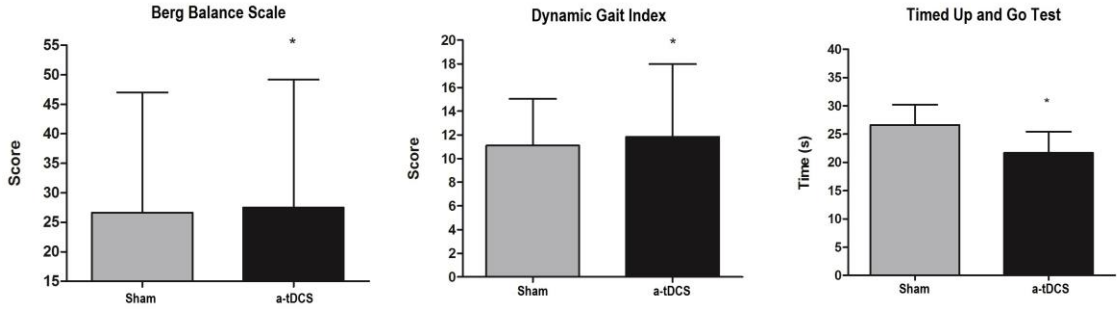

Table 1. Participants' characteristics

Sociodemographic Characteristics	
Gender (male / female)	13 / 4
Age (years)	69.18 ± 9.98
Education Level	
Elementary School	1
Middle School	5
High School	7
Higher Education	4
Clinical Characteristics	
Disease Duration (years)	7.06 ± 2.70
Hoehn & Yahr Scale	2.35 ± 1.06
UPDRS-III	18.0 ± 8.96
Medication	
Levodopa Only	7
Levodopa + Dopamine Agonist	4
Levodopa + Other	5
*Other**	1
Levodopa (mg/day)	635.94 ± 231.66
Dopamine Agonist LED [mg/day; 29]	87.00 ± 38.11
Total LED [mg/day; 29]	748.29 ± 343.80

UPDRS-III: motor domain of the Unified Parkinson's Disease Rating Scale; **LEP:** Levodopa Equivalent Dose; * Neither levodopa or dopamine agonist.

Anodal Transcranial Direct Current Stimulation (a-tDCS) on the Dorsolateral Prefrontal Cortex of Individuals with Parkinson's Disease