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ORIGINAL ARTICLE

Effects of transcranial direct current stimulation (TDCS) during a virtual reality task in individuals with parkinson's disease: a randomized, placebo-controlled, and triple-blind Clinical Trial

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Abstract

Introduction: Parkinson's Disease is a progressive neurological disorder resulting from the death of dopamine-producing cells in the substantia nigra. People with Parkinson's disease require effective rehabilitation therapies to control the motor symptoms that are commonly associated with this disease. Transcranial current direct stimulation is a promising tool to enhance sensorimotor functioning in people with Parkinson's disease, and the combination of transcranial current direct stimulation with Virtual Reality tasks is being explored in motor functioning, however, there is still a lack of evidence.

Objective: compare the motor performance between an active or sham single session of transcranial direct current stimulation combined with a Virtual Reality task in individuals with Parkinson Disease.

Methods: a triple-blinded randomized controlled trial protocol was performed. Fifty-four individuals with a Modified Hoehn & Yahr Scale rating from 1 to 4 were recruited. Individuals were randomly assigned to the following groups: active Transcranial Direct Current Stimulation (Transcranial Direct Current Stimulation + Virtual Reality task) or (sham Transcranial Direct Current Stimulation + Virtual Reality task). The protocol was performed in 18 minutes consisting of the following blocks: (5 minutes of initial rest stimuli, 4 minutes of the Transcranial Direct Current Stimulation + Virtual Reality task for Upper Limbs, 4 minutes of the Transcranial Direct Current Stimulation + Virtual Reality task for Lower Limbs, and 5 minutes of final rest stimuli). The active Transcranial Direct Current Stimulation protocol included low-frequency Transcranial Direct Current Stimulation with an intensity of 2 milliamperes (mA) over the primary cortex (M1) area of the dominant side of the brain.

Results: a significant effect for Groups and Blocks was found considering the measures of absolute and variable errors. Both active and sham Transcranial Direct Current Stimulation groups showed improvement in Upper Limb performance compared to Lower Limb performance.

Conclusion: active Transcranial Direct Current Stimulation could be an effective tool for enhancing motor performance during a Virtual Reality task. This may involve improved accuracy and precision of movement in both the Upper and Lower Limbs of individuals with Parkinson Disease. Positive effects in the active Transcranial Direct Current Stimulation were noticeable, even with a single session of Transcranial Direct Current Stimulation. In future research, investigation of the effect of a longer-term protocol is recommended, including follow-up measures.

Keywords: Parkinson's Disease, TDCS, Virtual Reality.

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Authors summary

Why was this study done?
This study was conducted to explore whether combining transcranial direct current stimulation (tDCS) with Virtual Reality (VR) tasks could improve motor performance in individuals with Parkinson’s Disease (PD). Although tDCS has shown potential to enhance sensorimotor function, and VR is increasingly used for motor rehabilitation, there is still limited evidence on the combined effect of these two approaches in people with PD.

What did the researchers do and find?
The researchers carried out a triple-blinded randomized controlled trial involving 54 participants with PD. Participants were randomly assigned to either an active tDCS + VR task group or a sham tDCS + VR task group. Each session lasted 18 minutes and included rest and task phases for both upper and lower limbs. The results showed significant improvements in motor performance, measured through absolute and variable errors. Both groups improved, but the active tDCS group demonstrated greater enhancement, particularly in upper limb performance compared to lower limb performance.

What do these findings mean?
These results suggest that active tDCS, when combined with VR-based motor tasks, can enhance motor performance in individuals with Parkinson’s disease. The improvements in accuracy and precision, even after a single session, indicate that tDCS may facilitate motor learning and control. This supports the potential use of tDCS as a complementary rehabilitation tool and highlights the need for long-term studies to confirm sustained benefits and understand the underlying mechanisms.

Highlights
The study investigated the combined use of transcranial direct current stimulation (tDCS) and Virtual Reality (VR) tasks in individuals with Parkinson’s disease (PD).
Motor performance improved in both active and sham tDCS groups, with greater enhancement observed in the active tDCS group, especially for upper limb performance.
Positive effects were observed after a single session of active tDCS.
The findings suggest that tDCS may be an effective adjunct therapy to improve motor control and precision in PD rehabilitation.
Long-term studies and follow-up assessments are recommended to confirm sustained benefits and determine optimal treatment protocols.

INTRODUCTION

Parkinson’s Disease (PD) is a chronic neurological and progressive disease resulting in the death of dopaminergic cells in the substantia nigra[1]. The basal ganglia (BG) are responsible for motor sequencing, motor skills, complex actions, modulation of higher-order cognitive functions, and mood regulation, and dopamine plays an important role in preserving these functions[2]. The principal manifestations of PD are motor dysfunctions such as bradykinesia, resting tremors, rigidity, and postural instability[3]. During the progression of the disease, non-motor symptoms may develop, such as cognitive and psychological decline, speech difficulties, sleep disorders, constipation, and erectile and urinary dysfunctions[4]. Even though treatments with pharmaceutical therapies can ease PD-related symptoms, in later stages of the disease these medications are prescribed in higher dosages, leading to unwanted side effects[5] and postural instability, however, the therapeutic effects are still unclear[6]. Non-pharmaceutical therapeutic interventions, such as rehabilitation can also help to maintain or improve motor symptoms, balance, gait, and functionality[7]. The main objective of rehabilitation for these individuals is to minimize the primary and secondary motor symptoms of the disease, which consequently helps the patient maintain independence, enhances the performance of daily living activities, and improves quality of life[8].

It is well-established that rehabilitation has a positive role in maintaining motor performance in people with PD[9-12]. The introduction of Physical Therapy (PT) showed benefits in strength[13], functional mobility[14], gait-related mobility, such as speed and step size[15,16], and balance[17,18].

Among the various rehabilitation possibilities, Virtual Reality (VR) is currently used as a tool to improve both the motor and cognitive functions of people with PD[19-21]. It is important to emphasize that VR can also enable the individual to learn new complex functional tasks that may involve planning, including daily activities such as riding public transport, shopping in the market, and driving[22]. Enhanced engagement, motivation, and attention are among the important potential benefits of VR and can contribute to increasing the interest of individuals in rehabilitation and increasing the intensity of practice[23,24]. Although there are some benefits from using VR alone in people with PD, recent studies have encouraged combining interventions and technologies as a promising rehabilitation option[25,26].

Non-invasive brain stimulation (NIBS) techniques, including transcranial direct current stimulation (tDCS), are neuromodulatory interventions. Considering combined interventions, these techniques are currently being used to treat PD symptoms[27-29] and can be combined with VR practices[25]. tDCS is a NIBS with low-frequency electrical stimulation, that can alter neuronal activity depending on the polarity of the stimulation, using electrodes placed on the scalp[30]. The electrodes used in the tDCS stimulation have anode and cathode polarities which change the resting state of the membrane cells of the surrounding region, which can modulate and potentially stimulate brain networks, depending on the target area and the polarity of the stimulation[26,31]. tDCS has already been used as a treatment to control motor symptoms of Parkinson’s Disease and other movement disorders, such as dystonia[32], Parkinson’s Plus[33], and Cerebellar Ataxia[34].

A large number of studies that involved healthy individuals and people with other neurological pathologies showed better and longer-lasting improvement in motor performance when tDCS was applied combined with other types of rehabilitation tools, such as treadmill training, working memory training, physical exercises, and intensive speech therapy, among others[35-38].However, despite the potential for combining interventions, no studies have investigated the combined effects of tDCS and VR to promote motor performance in individuals with PD.

It was organized a protocol using tDCS and VR to identify the possible benefits of this combined therapy. Hence, we evaluated individuals with PD who were divided into 2 groups (one group performed a VR task with active tDCS (Active Group) and the other group used the same VR task, but with sham tDCS (Sham Group). Both groups performed a coincident timing task using software on a computer.

In this trial, we hypothesized that all participants with PD would present improved performance after practicing the coincident timing task in a non-immersive VR using upper and lower limbs and that individuals with tDCS stimulation would present greater improvement when compared with the sham tDCS. Moreover, we expected that all participants would enjoy practicing the VR task, identified using an enjoyment scale. If these hypotheses were confirmed, the results of the present study would be relevant for the treatment of people with PD.

METHODS

The trial was carried out according to CONSORT guidelines for Pilot and Feasibility Studies https://www.equator-network.org/reporting-guidelines/consort-2010-statement-extension-to-randomised-crossover-trials/.

Design

This is a randomized, placebo-controlled, and triple-blind study conducted from May 2019 to February 2020. Participants who met the eligibility criteria were randomly assigned to 2 groups: Active tDCS + VR and Sham tDCS + VR.

Ethics committee and regulatory approval

This research was approved by the Ethics Committee of the University of São Paulo, with registration number CAAE: 02908218.0.0000.5390. Resolution 466/2012 of the National Health Council of 10/10/1996, which regulates research involving human beings, and the Declaration of Helsinki (1996) were respected. Data were stored electronically in databases with restricted and secure access. Any severe side effects during the study were reported to the emergency services in the area.

Randomization and Blinding

Randomization was performed through a blinded electronic security file used to assign individuals to the groups. The investigator TDS was responsible for the computer-generated random assignment list, arranging patients in Groups (1 and 2). The participants, researchers who performed the intervention, and statisticians were blinded to the participants' group until the end of the data analysis. To ensure adequate blinding, participants were given codes and separated for the allocation process by a different investigator. Before each stimulation session, the researcher responsible for the stimulation received a code that programs the tDCS device to deliver 20 min of active or sham stimulation.

Participant Recruitment

Fifty-four individuals with PD, previously diagnosed by a neurologist, participated in this study. They were recruited through social media, such as Facebook, Instagram, and WhatsApp groups. The researchers responsible for the study sent flyers through social media to advertise the study, and potential participants contacted them to establish a day to apply the intervention.

Inclusion Criteria

Participants were included if they: (a) had a previous diagnosis of PD confirmed by a specialist; (b) agreed to participate in the study with a term signed by themselves; (c) did not use a wheelchair; (d) was able to stand without any type of aid (such as canes and crutches) (Modified Hoehn & Yahr Scale from 1 to 4); (e) had good visual and auditory acuity; (f) presented no other pathology of neurological, orthopedic, or cognitive origin (observed by the Mini Mental State Examination MMS Escale); and (g) did not use Deep Brain Stimulation (DBS) or have any contraindications to tDCS.

Exclusion Criteria

Patients were excluded from the study if they: (a) were unable to understand the proposed VR task – assessed after 2 minutes of practice, or (b) dropped out of the protocol during practice due to fatigue or major imbalance.

Primary outcome (Absolute and Variable Error)

The MoveHero game verifies two important movement errors: 1) absolute error (AE), which demonstrates the accuracy of the movement, and 2) variable error (VE), which identifies the precision of the movement[39]. The specifications of the instrument will be examined below.

Instruments

MoveHero

In the current study, we used a platform called MoveHero, available for free use in Portuguese https://movehero.com.br/ and English https://movehero.com.br/en/. The patient was required to access the Internet to create their account, insert their name and email, and create a password (all data were collected in the software system and only the principal investigator had access). The platform presents different levels of difficulty, so after the participants had connected to the platform, the researcher directed them to the protocol developed for this research, which will be described below.

Presented by Martins *et al.*[40], MoveHero is considered a coincident timing task and presents several spheres falling down the computer screen, with a musical rhythm to increase engagement. The participant is positioned in front of a computer and when the game starts the webcam captures their movements, which are represented on the computer screen by an avatar. The goal of the game is to intercept all falling spheres, using upper or lower limbs, at the exact moment the spheres reach their specific target at the bottom of the computer screen. When the player uses the lower limbs they execute an abduction of the hips to reach the targets and when they use the upper limbs they execute a wave movement of the arms. The game presents four columns with fixed parallel targets allocated at two height levels (*e.g.*, two on the left - targets A and B; two on the right – targets C and D). The game also provides sensory feedback (visual – hit and miss feedback; auditory – anticipatory and delay error) – If the individual intercepts the sphere correctly, the game presents feedback by the sphere changing the color of the target to blue, with little stars around it (hit information). On the other hand, if the participant does not intercept the sphere correctly, the sphere changes color to red and the letter X appears inside the target (missing information) together with a sound indicating an error.

Software Score

During the game, the participant can follow their score, determined by the number of spheres hit (i.e., the information from each sphere hit appears in the bottom left side of the screen at all times) and at the end of each game, the participant receives feedback with their total score (when the game is finished a total score appears in the middle of the computer screen).

Intervention with tDCS

Active tDCS and Sham tDCS were performed in a single session combined with the VR task. The frequency used was 2mA and the stimulation intensity was programmed to 100%. The electrode corresponding to the positive side (anode) was positioned in the M1 cortical area (primary motor cortex) in the dominant hemisphere, and the negative electrode (cathode) was positioned in the contralateral supraorbital area. For the sham stimulation, the electrodes were placed in the same position and an active current was initiated with ramping up and down for 30 seconds to simulate the real stimulation. A saline-soaked 35 cm² (5×7cm) sponge with electrodes was placed on the patient's scalp and secured with adjustable rubber straps. The sponge placement follows the 10–20 EEG system. All the patients were aware of the side effects every day, according to international safety guidelines[41]. The device used was NeuroConn's DS-Stimulator, which allows blinding of individuals and researchers.

Procedures

The patients were contacted by telephone and asked if they were interested in participating in the study. If they agreed, they received the Free and Informed Consent Form to fill out, and the inclusion criteria were checked. The researcher applied a brief anamnesis to collect personal and sociodemographic data. After the anamnesis, the researcher applied the scales, and then the tDCS equipment was prepared. First, the circumference of the skull it was measured with a tape measure, and then the researcher asked the patient to indicate their dominant cerebral hemisphere (for correct positioning on the skull). The tDCS was administered by an experienced professional and according to pre-established methods of management in the adult population[41]. Positioning was the same for the active and sham tDCS, and two square sponges soaked in saline were placed on the skull and fixed with a plastic band. The active (anodic) tDCS was performed with electrodes of 25-35cm^2, an intensity of 2mA, a rise and fall ramp of 30 seconds, and a density of 0.057mA/cm^2. The anodic electrode was positioned in the M1 area in the dominant hemisphere, which was previously observed by Fregni *et al.*[42] who reported that it could be an important target for brain stimulation in individuals with PD. Lang *et al.*[43] showed that anodic tDCS in the primary motor cortex induces an increase in basal ganglia activity. The cathode electrode was positioned in the contralateral supraorbital area. The sham tDCS had the same procedures as the active, but the current was interrupted after 30 seconds of stimulation. This configuration ensured that the stimulus would be stopped after generating a considerable stimulus, while the other features of the intervention were maintained.

After correct positioning of the tDCS equipment, a protocol-blind researcher configured the equipment according to a code (previously provided by a 3rd researcher, who established the codes that would be active and sham) and induced the initial stimulus of 5 minutes (at rest, while the patient was sitting). Meanwhile, another blind researcher placed the notebook (14 inches) on a table (the participant was 1.5 m away from the screen) adjusted according to the patient's height (the taller the individual, the higher the placement of the computer), and set the game to launch. Immediately after the setup, the researcher explained the game to the patient. It is important to emphasize that the participants had no previous contact with the MoveHero game. The researcher started the MoveHero game and remained behind the patient to avoid any imbalance.

The VR task was performed in 2 attempts (4 minutes each) totaling 8 minutes of practice. In the first 4 minutes, the participants used the upper limbs to intercept the spheres (4 targets) (Figure 1). In the final 4 minutes, the participants used the lower limbs (for the 2 most proximal targets - the distal targets were too far away to be reached with leg abduction) (figure 2). To play with the lower limbs, the researcher angled the computer screen so the camera could focus only on the patient's lower limbs. The players' heart rate was monitored throughout the protocol and if they were unable to perform the VR task for the whole 8 minutes of practice (due to fatigue or severe postural instability), the game was interrupted, and the patient rested for a few minutes. They were then asked if they were willing to continue playing; if not, the patient was excluded from the study, and if so, the researcher continued the game from the moment they had previously stopped.

After 8 minutes of tDCS + VR, participants received 5 minutes of final resting stimulus, totaling 18 minutes of stimulation (approximately 20 minutes), which is the time used in studies with anodic tDCS in people with PD by Schoellmann *et al.*[29] and Doruk *et al.*[44] After the end of the session, participants were asked about the presence of adverse effects and assigned a score for the game ranging from 0 to 4, with 0 indicating a "Very Boring" game, 1 "Boring", 2 "Somewhat Fun", 3 "Fun", and 4 "Great Fun".

Figure 1: Participant positioning and game design with upper limbs
Source: From the author.

Figure 2: Participant positioning and game design with lower limbs
Source: From the author.

Data Analysis

We considered the Absolute Error (AE) and Variable Error (VE) as dependent variables. The MoveHero game performs the measurements in milliseconds to demonstrate the movement accuracy and identify the precision of the movement, respectively. The hit attempts of the targets in the game MoveHero were transformed into 3 blocks of attempts, by dividing the total of 4 minutes into 3 (1.3 minutes in each Block) to evaluate if there was an improvement from the first Block (B1) to the second Block (B2) and the third Block (B3). In this way, we were able to evaluate whether the first attempts were better than the later ones. Multivariate Analysis of Variables (MANOVA) was applied to compare active and sham tDCS, with repetitive measures for "Blocks" and "Limbs" (Upper Limbs and Lower Limbs). Values were considered significant with $p<0.05$. The data in the graphics are represented as mean and standard error. Partial Eta squared ($\eta 2$) was reported to measure the effect size and interpreted as a small (effect size >0.01) medium (effect size >0.06) or large effect (effect size >0.14). The statistical package used was SPSS (IBM Corporation, Armonk, NY, United States) version 20.0.

RESULTS

Table 1 presents the mean values for age, weight, height, Mini BESTest, BBS, Mini-Mental Test, and MDS-UPDRS, as well as the dispersion values. The inferential analysis showed that the groups were homogeneous in these variables. There were differences between the total value of the MDS-UPDRS scale, in the Upper Limbs section of the UPDRS, which consists of the separate analysis of items 20 to 25 of the scale45 and subsections of the UPDRS (Part III, IV A, and VI C) (Table 1).

Initially, 68 participants agreed to participate in the study and underwent detailed screening using the eligibility criteria. A total of 54 individuals (20 women and 34 men) participated in the study, 25 in the active tDCS (mean age = 62.2 ± 11.1 years) and 28 in the sham tDCS (mean age = 66.3 ± 7.2 years). On the Hoehn & Yahr scale, 2% of patients were in stage 0 (1 patient in the sham tDCS), 31 patients in stage 1 (57%) (18 - active tDCS 69%; 13 - sham tDCS 46 %), 11 patients in stage 2 (20%) (4 - active tDCS 15%; 7 - sham tDCS 25%), 8 patients in stage 3 (15%) (3 - active tDCS 12%; 5 - sham tDCS 18%), and 3 patients in stage 4 (6%) (1 - active tDCS 4%; 2 - sham tDCS 7%).

Table 1: Characterization of the groups

	Active tDCS	Sham tDCS	
	Mean ± SD	Mean ± SD	P value
Age (years)	62.2 ± 11.1	66.3 ± 7.2	0.110
Height (meters)	1.69 ± 0.08	1.65 ± 0.08	0.056*
Mini Best Test	25.8 ± 4.9	23.8 ± 7.5	0.255
BERG	52 ± 5	47.7 ± 12.1	0.100
Mini Mental Test	26.7 ± 3.3	25.9 ± 3.5	0.397
MDS-UPDRS Part I	3.6 ± 2.5	3.2 ± 2	0.528
MD-UPDRS Part II	10.3 ± 4.5	13.4 ± 6.8	0.061
MDS-UPDRS Part III	10.7 ± 6.3	14.2 ± 6.3	0.049*
MDS-UPDRS Parte IV A	1.2 ± 1.4	2.3 ± 1.9	0.022*
MDS-UPDRS Parte IV B	1.3 ± 1.4	1.7 ± 1.6	0.440
MDS-UPDRS Parte IV C	0.6 ± 0.6	1 ± 0.8	0.055*
MDS-UPDRS Total	28 ± 12.2	36 ± 14.5	0.034*
MDS_UPDRS Upper Limbs	4.35 ± 3.0	6.82 ± 2.4	0.002*

Anti-Parkinsonism Medication

Table 2 presents the anti-parkinsonian drugs that the patients used. The medications observed were Levodopa (L-dopa), COMT Inhibitors, Anticholinergics, Cannabidiol Oil, MAO-B Inhibitors, Dopamine Agonists, Amantadine, and Antidepressants. A total of 50 of the 54 patients were taking Levodopa (L-Dopa) medication (93%) (25 - active tDCS 96%; 25 - sham tDCS 89%).

MANOVA analysis showed significant effects for Groups [Wilk's lambda: 0.773; F2, 50= 7.34; p= 0.002, ηp2= 0.23, op= 0.92], Limbs [Wilk's lambda: 0.663; F2, 50= 12.7; p< 0.001, ηp2= 0.34, op= 0.99], and Blocks [Wilk's lambda: 0.523; F4, 48= 11; p< 0.001, ηp2= 0.48, op= 1.0]. There were no significant effects for the Positions factor or significant interactions between factors. Separate ANOVAs are presented below.

Table 2: Number of patients who were using each Anti-Parkinsonism medication

Anti-Parkinsonism Medications			
	Active tDCS n=26	Sham tDCS n=28	Total n=54
	N (%)	N (%)	N (%)
COMT Inhibitors	1 (4%)	3 (11%)	4 (7%)
L-Dopa	25 (96%)	25 (89%)	50 (93%)
Anticholinergic	2 (8%)	2 (7%)	4 (7%)
Canabidiol	2 (8%)	0 (0%)	2 (4%)
MAO-B Inhibitors	1 (4%)	3 (11%)	4(7%)
Dopamine Agonists	10 (38%)	15 (54%)	25 (46%)
Amantadine	5 (19%)	7 (25%)	12 (22%)
Antidepressants	11 (42%)	11 (39%)	22 (41%)

Motor Performance

Absolute Error - AE

Significant main effects were found between Groups [F1, 51 = 4,43; p = 0.040, ηp2 = 0.08, op = 0.54], Limbs [F1, 51 = 17.72; p <0.001, ηp2 = 0.26, op = 0.98] and Blocks [F2, 102 = 9.0; p <0.001, ηp2 = 0.15, op = 0.96]. This result indicates that all groups presented improved performance with practice, verified through the improvement in the absolute errors between blocks. The active tDCS significantly improved the absolute error from Block 1 (m = 544 ms) to Block 3 (m = 450 ms; p = 0.006), and from Block 2 (m = 518 ms) to Block 3 (m= 450 ms p = 0.006). The sham tDCS significantly improved the absolute error from Block 1 (m = 650 ms) to Block 2 (m = 571 ms; p = 0.015) and from Block 1 to Block 3 (m = 565 ms; p = 0.009). Moreover, the active tDCS had a lower overall absolute error (m = 505 ms) than the sham tDCS (m = 596 ms) and this difference was more evident in the lower limb (i.e., the active tDCS showed a lower absolute error with the Lower Limbs when compared to the sham tDCS (p = 0.05), but not with the Upper Limbs.

Variable Error - EV

Significant main effects were found in the Groups [F1, 51 = 11,80; p = 0.001, ηp2 = 0.18 op = 0,92], Limbs [F1, 51 = 23,3; p <0.001, ηp2 = 0.31, op = 0.99], and

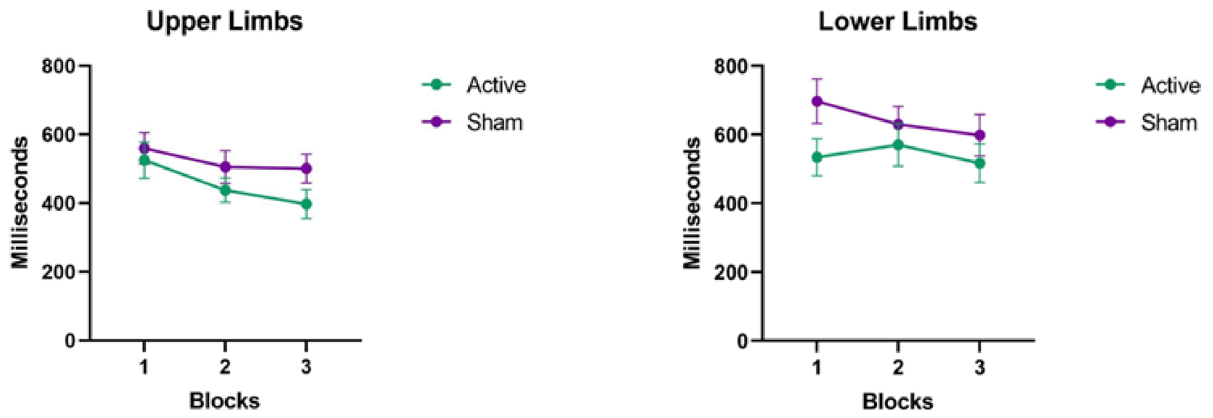

Figure 3: Graphic representation of Absolute Error for active and sham tDCS

Blocks [F2, 51 = 21; p <0.001, ηp2 = 0.29, op = 1.0]. This result indicates that the active tDCS presented a lower overall variable error (453 ms) when compared to the sham tDCS (576 ms), with a significant interaction between Limbs and Blocks [F2, 51 = 3.2; p = 0.047, ηp2 = 0.60, op = 0.60]. The active tDCS showed a lower variable error with Upper Limbs (p = 0.010) and Lower Limbs (p = 0.003) when compared to the sham tDCS. Regarding the Blocks, the active tDCS significantly improved the variable error from Block 1 (m = 501 ms) to Block 3 (m = 389 ms; p <0.001) and from Block 2 (m = 470 ms) to Block 3 (p = 0.003). The sham tDCS significantly improved the variable error from Block 1 (m = 652 ms) to Block 3 (m = 534 ms; p <0.001) and from Block 1 to Block 2 (m = 543 ms; p< 0.001).

Enjoyment

The chi-square test did not present significant results for the Enjoyment score when comparing groups. Most participants within the two groups classified the game as “fun” or “great fun” (94.4%). Only 5.6% of the sample rated the game as “somewhat fun” and no patients rated the game as “boring” or “very boring”.

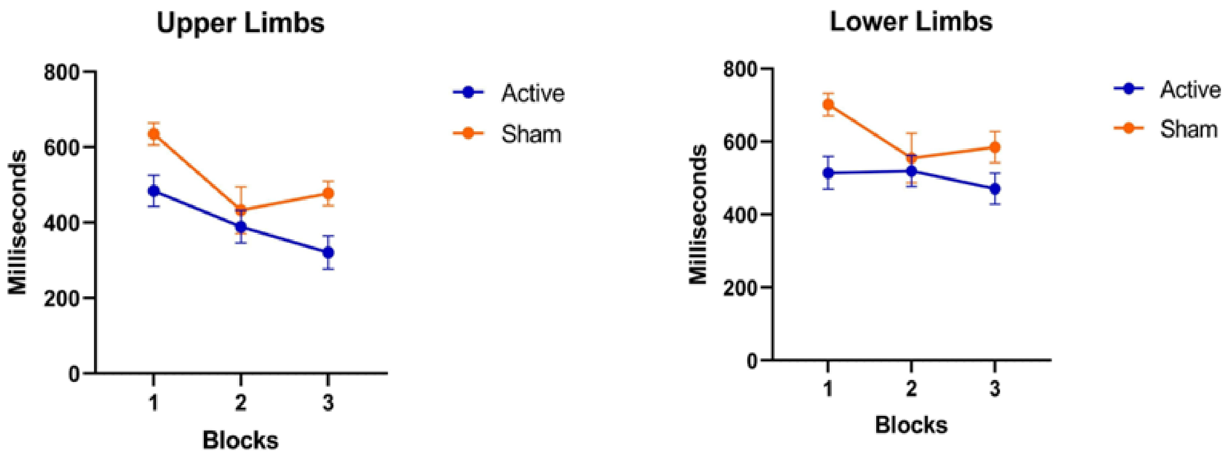

Figure 4: Graphic representation of Variable Error for active and sham tDCS

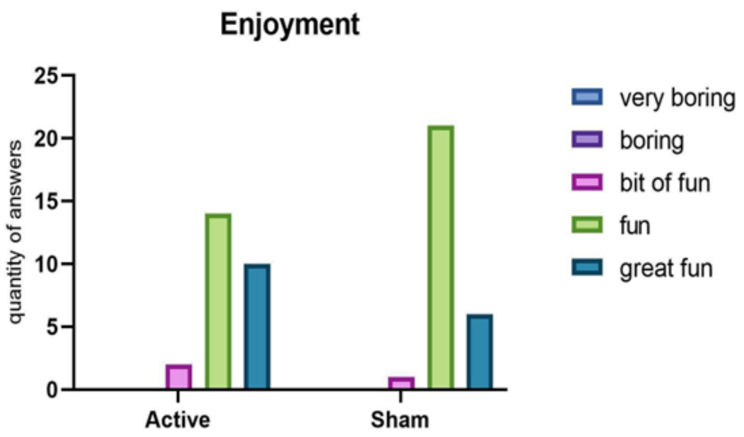

Figure 5: Graphic representation of the frequencies of each enjoyment score.

DISCUSSION

This randomized clinical trial assessed the effectiveness of a single tDCS session on the performance of a VR task in people with PD and our results partially confirmed our hypothesis. All participants (active and sham tDCS groups) with PD presented improved performance with practice using the upper and lower limbs in a VR task and the active tDCS presented better improvement when compared with the sham tDCS, as hypothesized. However, this difference was more evident in the practice with the lower limbs. Moreover, all participants enjoyed practicing the VR task, rating the game as "fun" or "great fun". These results will be and more fully examined below.

Performance during Virtual Reality

In the present study, both groups showed improvement in performance in the timing coincident task. The active and sham tDCS demonstrated significant differences, with improvement in performance between Blocks for the AE (accuracy) and for the VE (precision), indicating positive use of the VR task among individuals with PD. Several studies have used VR as an alternative for rehabilitation, finding positive results for motor function[46,47], balance and coordination[48,49], cognitive function, mental health[50-52] and increased UPDRS scores[51].

The performance improvement may probably be directly related to the various benefits that VR provides, such as the offer of continuous feedback throughout the practice of the game, grading of training intensity, increasing visual, sensory, and auditory feedback, and the possibility of stimulating motor and cognitive aspects with a motivational and engaging environment[53].

VR can be an effective tool for the rehabilitation of patients with neurological diseases, by promoting experiences and challenges in a personalized way, since they perform the tasks repeatedly, with continuous feedback and motivation[54,55]. Thus, we agree with Dias *et al.*[38] that Repetition, Feedback, and Motivation could be the three main factors in improving performance using a VR task. The VR game provided positive feedback and motivational tasks (using music and colored objects). Considering feedback, the participant hits the target, promoting an engaging environment, and maintaining player motivation and participation, which may have contributed to the progressive improvement in game performance[56]. According to Villiger *et al.*[57], several sensorimotor neuronal circuits can be increased when an individual performs a task with high motivation and engagement, and due to dopaminergic denervation in PD, any potential aspects that cause demotivation, such as negative feedback, should be avoided, which may reduce the adherence of players to the task[58]. Recent studies of functional brain connectivity show that learning in PD can benefit from a reward-based approach[59].

In the secondary analyses, our results showed that in both groups the majority of the enjoyment scores remained in the "fun" and "great fun" levels on all the intervention days. Although there was no difference between the sequences, we can speculate that having fun while playing and performing a VR task enhanced the possibility of the individual becoming more committed to rehabilitation through individualized training, and also to becoming more involved by allowing themselves to experience different types of environments through sensors and receiving feedback, especially on their audio-visual senses[60].

We can speculate that the music played in the background, and the colored spheres could be also motivational factors that contribute to improved performance and transform the therapy into a playful environment[61]. The same musical rhythm was offered to all participants in the present study. Playing music in the background may have contributed to the improvement in performance during the proposed task, as listening to music improves neuronal connectivity in specific regions of the brain of healthy participants, and musical activities promote neural plasticity and induce gray and white matter alterations in various regions of the brain, especially in areas of the frontal and temporal lobes[62-64].

According to the meta-analysis by Triegaardt *et al.*[21], the exact mechanisms by which VR improves the motor performance of individuals with PD are not yet fully understood. Nevertheless, studies have shown that patients can learn motor skills in virtual environments and that these are easily implemented in real life[65].

Combined Intervention

Considering the use of VR and tDCS, our results demonstrated that the individuals in the active tDCS presented significantly greater improvement than the sham tDCS. This indicates that performing the task while receiving tDCS therapy could help patients progressively improve during the game practice. During the timing coincident task used, 8 minutes, the patients improved from one block to the next, despite this being their first contact with the game.

There are still many uncertainties surrounding the neurophysiological mechanism of tDCS[66]. Nevertheless, a meta-analysis by Chase *et al.*[67], reveals growing confidence in this method, describing the impact on neural activity and behavior, including motor thresholds, prefrontal cortex-related cognition, and depression. According to this recent meta-analysis, available data from animal and human studies suggest that the parameters used in humans currently modulate neural activity through changes in electrical fields and neural oscillations, rather than triggering neuronal spikes. tDCS can increase ventral posterolateral thalamic nucleus activity and can influence basal ganglia function[67]. Furthermore, anodic tDCS over the motor cortex alters the resting membrane potentials of underlying neurons, leading to increased cortical excitability, with immediate and long-term effects that have been proposed to help improve motor skills[68].

As tDCS has a modulating role in neural activity and with the various studies in the field that have been growing exponentially[69], a meta-analysis identified that tDCS is more effective when the goal of therapy is for the individual to learn a new task, rather than to improve performance in a previously learned task[70].

People with PD face difficulties in consolidating new motor skills, and electrostimulation techniques can optimize neuronal circuits, and even increase compensatory mechanisms of cortical excitability, thus facilitating the acquisition of new motor skills[71,72.] Evidence suggests that the use of combination therapies can bring greater and longer-lasting benefits in motor functions than therapies performed in isolation in healthy people[73]. A systematic review carried out by Massetti *et al.*[25] noted that overall, combined tDCS + VR therapies show positive effects in diverse populations (cerebral palsy, healthy people, and individuals who have had a stroke) and evidence regarding the frequency and duration of therapies is still uncertain as well as specific targeting for each pathology.

Techniques such as tDCS have shown some success when combined with VR therapies, as in the study by Ang *et al.*[74] who used this approach with people affected by a cerebrovascular accident (CVA) to facilitate motor imagination, obtaining positive results. Currently, models and protocols for determining tDCS assemblies are not yet fully elucidated, so investigations of the functioning of brain activity during the performance of a cognitive or motor task in a VR task still need to be elaborated in more depth to better define the pattern of cortical excitation induced by tDCS[75].

The application of tDCS and the contact of individuals with the proposed task was carried out on only one day. The neurophysiological effects of tDCS, such as promoting synaptic plasticity and inducing lasting changes in excitability in the central nervous system, could not be thoroughly evaluated in just one day of application, even though positive effects were found[42]. In summary, there are still many open questions about the effects of tDCS applications on brain oscillations and the relationships that these effects may have on human brain functioning. To our knowledge, the first test to promote improvement in the patient's motor function with PD using the combination of tDCS + VR was conducted by Harris *et al.*[76]. Therefore, the use of combined tDCS + VR therapy is still very recent. This study will contribute to observing the behavior the motor performance of individuals with PD when submitted to this combined therapy and support further longer-term trials.

Improvement in upper and lower limbs

Individuals with PD deal with difficulty in the control of movements, such as reaching and grasping due to motor disorders in the upper limbs related to the disease, which leads to slow execution of tasks that require a complex pattern of movements[77]. On the other hand, people with PD face other symptoms of the lower limbs, such as postural instability, balance problems, and gait disorders, which trigger falls and injuries, leading to difficulty performing daily life activities[3]. In this protocol, the task proposed had a high demand for both limbs and the fact that both groups presented improved scores for the two types of demand can predict that this task is effective for symptoms related to PD in both upper and lower limbs. However, we observed that this was more evident in the practice with the lower limbs considering the absolute error (i.e. our results showed improvement in the variable error for both upper and lower limbs, but for the absolute error we only observed improvement in the lower limbs).

We can only speculate that the fact that in the upper limb task (performed first) the player needed to always be in a standing position and move in different directions, this postural demand could facilitate the subsequent lower limb practice and influence the participant's performance. It is well known that due to the basal ganglia dysfunction in PD, dysregulation of the anticipatory and feed-forward precision mechanism affects motor performance[78]. The studies of Jansen *et al.*[79] presented a positive influence on the upper limb task when PD individuals practiced previous lower limb activities. The authors proposed that this could be influenced by exercises such as cycling and can modify the connectivity and function of the interaction between basal ganglia and cortical motor areas, by facilitating the function of these structures, which results in more coordinated and efficient bimanual movements[80]. We propose that the opposite should also be considered.

Thus, practicing an upper limb task in a standing position could positively influence the performance of the task performed with the lower limbs. Considering this supposition, the order of practice could be considered a first limitation of our study, but also an indication that future studies should be performed comparing the order of practice (upper or lower limbs) and its influence on motor performance.

Limitations and Future Studies

There are limitations to this study. (1) The protocol was for only one day, and it is important to observe if this progressive improvement in performance remains in the long term. Because this is a one-day protocol, we can speculate that a long period of practice (more days practicing the same VR task) would be positive for learning how to use the feedback given by the game and could cause greater automation of movement, with a more evident improvement in performance, which is actually what happens with VR games; if an individual practice a certain task, performance tends to improve progressively[38]; (2) The analysis performed in the present study focused mainly on motor skills, but it would be interesting to psychologically analyze the participants to observe possible changes in mood and behavior after the game; (3) In our protocol, the music played during the game was pre-selected by the researcher. Sihvonen *et al.*[61] in a systematic review noted that most studies do not use music selected by the patient, however, due to the strong emotional factors involved in music, perhaps allowing the patient to choose their music during therapy would bring more benefits, as the music chosen by the patient could have some effect; and (4) Our findings support that a VR task designed for individuals with neurological disorders can be beneficial to motor performance in people with PD, but we did not compare this with a conventional and commercial game. Future studies should compare games available commercially with VR tasks projected for people with disabilities.

More details on the efficacy, safety, feasibility, and adherence of VR rehabilitation should be obtained and examined through more randomized controlled trials, directly specifying the goals to be achieved with a given type of intervention, game, or VR activity. The current evidence indicates that training protocols with VR are similar to non-VR-based training for people with PD, it is up to the therapist to precisely analyze the advantages and disadvantages of this approach and prescribe the intervention accordingly. There is also a great need to identify the profile of the specific individuals with PD who would benefit from this practice[54].

Chuang *et al.*[81] suggested in a recent meta-analysis that future studies should elaborate specific VR tasks for people with PD since some types of technology available commercially can be too complex for this population. The present study used a VR game designed especially for people with neurological diseases, the MoveHero game, which has been used in other studies, with different populations, and showed improvement in motor performance[38,82].

Further studies should be carried out to investigate whether the effects of tDCS remain in subjects in the long term. The current study served as the basis for this future hypothesis, that the performance of subjects would continue to improve if they were exposed again to the combined application of tDCS and VR.

CONCLUSION

The active tDCS group performed better during the proposed task when compared to the sham tDCS, but both groups showed improved performance during the proposed task, both for accuracy (AE) and precision (VE). VR seems to be the future of rehabilitation for people with PD and its association with tDCS appears to be beneficial even after only one application. Studies with larger samples and with a prolonged period of treatment should be performed to establish whether these effects are maintained in the long term.

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REFERENCES

1. Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson’s disease. Lancet Neurol [Internet]. 2006 Jan;5(1):75–86. Available from: http://dx.doi.org/10.1016/S1474-4422(05)70285-4.
2. Riva D, Taddei M, Bulgheroni S. The neuropsychology of basal ganglia. Eur J Paediatr Neurol [Internet]. 2018 Mar;22(2):321–6. Available from: http://dx.doi.org/10.1016/j.ejpn.2018.01.009.
3. Bloem BR, Okun MS, Klein C. Parkinson’s disease. Lancet [Internet]. 2021 Jun 12;397(10291):2284–303. Available from: http://dx.doi.org/10.1016/S0140-6736(21)00218-X.
4. Hamani C, Lozano AM. Physiology and pathophysiology of Parkinson’s disease. Ann N Y Acad Sci [Internet]. 2003 Jun;991(1):15–21. Available from: http://dx.doi.org/10.1111/j.1749-6632.2003.tb07459.x.
5. Workman CD, Thrasher TA. The influence of dopaminergic medication on balance automaticity in Parkinson’s disease. Gait Posture [Internet]. 2019 May;70:98–103. Available from: http://dx.doi.org/10.1016/j.gaitpost.2019.02.015.
6. Visser JE, Allum JHJ, Carpenter MG, Esselink RA, Speelman JD, Borm GF, et al. Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinson’s disease. J Neurol [Internet]. 2008 Feb;255(2):205–10. Available from: http://dx.doi.org/10.1007/s00415-008-0636-x.
7. Smania N, Corato E, Tinazzi M, Stanzani C, Fiaschi A, Girardi P, et al. Effect of balance training on postural instability in patients with idiopathic Parkinson’s disease. Neurorehabil Neural Repair [Internet]. 2010 Nov;24(9):826–34. Available from: http://dx.doi.org/10.1177/1545968310376057.
8. Greenberg DA, Aminoff MJ, Simon RP, Finkelsztejn A, Müller R. Neurologia clínica. 5. ed. São Paulo: Artmed, 2005.
9. Radder DLM, Lígia Silva de Lima A, Domingos J, Keus SHJ, van Nimwegen M, Bloem BR, et al. Physiotherapy in Parkinson’s disease: A meta-analysis of present treatment modalities. Neurorehabil Neural Repair [Internet]. 2020 Oct;34(10):871–80. Available from: http://dx.doi.org/10.1177/1545968320952799.
10. Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson’s disease. Mov Disord [Internet]. 2018 Aug;33(8):1248–66. Available from: http://dx.doi.org/10.1002/mds.27372.

11. Kalia LV, Lang AE. Parkinson's disease. Lancet [Internet]. 2015 Aug 29;386(9996):896–912. Available from: http://dx.doi.org/10.1016/S0140-6736(14)61393-3.
12. Mak MKY, Hui-Chan CWY. Cued task-specific training is better than exercise in improving sit-to-stand in patients with Parkinson's disease: A randomized controlled trial. Mov Disord [Internet]. 2008 Mar 15;23(4):501–9. Available from: http://dx.doi.org/10.1002/mds.21509.
13. Ramazzina I, Bernazzoli B, Costantino C. Systematic review on strength training in Parkinson's disease: an unsolved question. Clin Interv Aging [Internet]. 2017 Mar 31;12:619–28. Available from: http://dx.doi.org/10.2147/CIA.S131903.
14. Delabary M, Komeroski IG, Monteiro EP, Costa RR, Haas AN. Effects of dance practice on functional mobility, motor symptoms and quality of life in people with Parkinson's disease: a systematic review with meta-analysis. Aging Clin Exp Res [Internet]. 2018 Jul;30(7):727–35. Available from: http://dx.doi.org/10.1007/s40520-017-0836-2.
15. Nieuwboer A, Kwakkel G, Rochester L, Jones D, van Wegen E, Willems AM, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. J Neurol Neurosurg Psychiatry [Internet]. 2007 Feb 1;78(2):134–40. Available from: http://dx.doi.org/10.1136/jnnp.200X.097923.
16. Lim I, van Wegen E, de Goede C, Deutekom M, Nieuwboer A, Willems A, et al. Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. Clin Rehabil [Internet]. 2005 Oct;19(7):695–713. Available from: http://dx.doi.org/10.1191/0269215505cr906oa.
17. Conradsson D, Löfgren N, Nero H, Hagströmer M, Ståhle A, Lökk J, et al. The effects of highly challenging balance training in elderly with Parkinson's disease: A randomized controlled trial: A randomized controlled trial. Neurorehabil Neural Repair [Internet]. 2015 Oct;29(9):827–36. Available from: http://dx.doi.org/10.1177/1545968314567150.
18. Canning CG, Sherrington C, Lord SR, Close JCT, Heritier S, Heller GZ, et al. Exercise for falls prevention in Parkinson disease: a randomized controlled trial. Neurology [Internet]. 2015 Jan 20;84(3):304–12. Available from: http://dx.doi.org/10.1212/WNL.0000000000001155.
19. Dockx K, Bekkers EM, Van den Bergh V, Ginis P, Rochester L, Hausdorff JM, et al. Virtual reality for rehabilitation in Parkinson's disease. Cochrane Database Syst Rev [Internet]. 2016 Dec 21;12(12):CD010760. Available from: http://dx.doi.org/10.1002/14651858.CD010760.pub2.
20. Lei C, Sunzi K, Dai F, Liu X, Wang Y, Zhang B, et al. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. PLoS One [Internet]. 2019 Nov 7;14(11):e0224819. Available from: http://dx.doi.org/10.1371/journal.pone.0224819.
21. Triegaardt J, Han TS, Sada C, Sharma S, Sharma P. The role of virtual reality on outcomes in rehabilitation of Parkinson's disease: meta-analysis and systematic review in 1031 participants. Neurol Sci [Internet]. 2020 Mar;41(3):529–36. Available from: http://dx.doi.org/10.1007/s10072-019-04144-3.
22. Simões M, Bernardes M, Barros F, Castelo-Branco M. Virtual travel training for autism Spectrum Disorder: Proof-of-concept interventional study. JMIR Serious Games [Internet]. 2018 Mar 20;6(1):e5. Available from: http://dx.doi.org/10.2196/games.8428.
23. Avola D, Cinque L, Foresti GL, Marini MR. An interactive and low-cost full body rehabilitation framework based on 3D immersive serious games. J Biomed Inform [Internet]. 2019 Jan;89:81–100. Available from: http://dx.doi.org/10.1016/j.jbi.2018.11.012.
24. Osumi M, Ichinose A, Sumitani M, Wake N, Sano Y, Yozu A, et al. Restoring movement representation and alleviating phantom limb pain through short-term neurorehabilitation with a virtual reality system. Eur J Pain [Internet]. 2017 Jan;21(1):140–7. Available from: http://dx.doi.org/10.1002/ejp.910.
25. Massetti T, Crocetta TB, Silva TD da, Trevizan IL, Arab C, Caromano FA, et al. Application and outcomes of therapy combining transcranial direct current stimulation and virtual reality: a systematic review. Disabil Rehabil Assist Technol [Internet]. 2017 Aug;12(6):551–9. Available from: http://dx.doi.org/10.1080/17483107.2016.1230152.
26. Cassani R, Novak GS, Falk TH, Oliveira AA. Virtual reality and non-invasive brain stimulation for rehabilitation applications: a systematic review. J Neuroeng Rehabil [Internet]. 2020 Oct 31;17(1):147. Available from: http://dx.doi.org/10.1186/s12984-020-00780-5.
27. Cucca A, Sharma K, Agarwal S, Feigin AS, Biagioni MC. Tele-monitored tDCS rehabilitation: feasibility, challenges and future perspectives in Parkinson's disease. J Neuroeng Rehabil [Internet]. 2019 Jan 31;16(1):20. Available from: http://dx.doi.org/10.1186/s12984-019-0481-4.
28. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol [Internet]. 2017 Jan;128(1):56–92. Available from: http://dx.doi.org/10.1016/j.clinph.2016.10.087.

29. Schoellmann A, Scholten M, Wasserka B, Govindan RB, Krüger R, Gharabaghi A, et al. Anodal tDCS modulates cortical activity and synchronization in Parkinson's disease depending on motor processing. NeuroImage Clin [Internet]. 2019 Jan 23;22(101689):101689. Available from: http://dx.doi.org/10.1016/j.nicl.2019.101689.
30. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol [Internet]. 2016 Feb;127(2):1031–48. Available from: http://dx.doi.org/10.1016/j.clinph.2015.11.012.
31. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev [Internet]. 2013 Sep;37(8):1702–12. Available from: http://dx.doi.org/10.1016/j.neubiorev.2013.06.014.
32. Bradnam LV, Graetz LJ, McDonnell MN, Ridding MC. Anodal transcranial direct current stimulation to the cerebellum improves handwriting and cyclic drawing kinematics in focal hand dystonia. Front Hum Neurosci [Internet]. 2015 May 18;9:286. Available from: http://dx.doi.org/10.3389/fnhum.2015.00286.
33. Alexoudi A, Patrikelis P, Fasilis T, Deftereos S, Sakas D, Gatzonis S. Effects of anodal tDCS on motor and cognitive function in a patient with multiple system atrophy. Disabil Rehabil [Internet]. 2020 Mar;42(6):887–91. Available from: http://dx.doi.org/10.1080/09638288.2018.1510043.
34. Benussi A, Koch G, Cotelli M, Padovani A, Borroni B. Cerebellar transcranial direct current stimulation in patients with ataxia: A double-blind, randomized, sham-controlled study: CEREBELLARtDCS IN ATAXIC DISORDERS. Mov Disord [Internet]. 2015 Oct;30(12):1701–5. Available from: http://dx.doi.org/10.1002/mds.26356.
35. Mousavi N, Nitsche MA, Jahan A, Nazari MA, Hassanpour H. Efficacy of transcranial Direct Current Stimulation (tDCS) combined with intensive speech therapy for language production in monozygotic twins with corpus callosum dysgenesis (CCD): A sham-controlled single subject study. Neurocase [Internet]. 2022 Apr;28(2):218–25. Available from: http://dx.doi.org/10.1080/13554794.2022.2071626.
36. Straudi S, Buja S, Baroni A, Pavarelli C, Pranovi G, Fregni F, et al. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. Clin Rehabil [Internet]. 2018 Oct;32(10):1348–56. Available from: http://dx.doi.org/10.1177/0269215518777881.
37. Collange Grecco LA, de Almeida Carvalho Duarte N, Mendonça ME, Galli M, Fregni F, Oliveira CS. Effects of anodal transcranial direct current stimulation combined with virtual reality for improving gait in children with spastic diparetic cerebral palsy: a pilot, randomized, controlled, double-blind, clinical trial. Clin Rehabil [Internet]. 2015 Dec;29(12):1212–23. Available from: http://dx.doi.org/10.1177/0269215514566997.
38. Dias ED, de Menezes LDC, da Silva TD, da Silva NM, Vidal PR, Brondane BR, et al. Comparison of cardiac autonomic modulation of athletes and non-athletes individuals with spinal cord injury at rest and during a non-immersive virtual reality task. Spinal Cord [Internet]. 2021 Dec;59(12):1294–300. Available from: http://dx.doi.org/10.1038/s41393-021-00722-5.
39. de Mello Monteiro CB, da Silva TD, de Abreu LC, Fregni F, de Araujo LV, Ferreira FHIB, et al. Short-term motor learning through non-immersive virtual reality task in individuals with down syndrome. BMC Neurol [Internet]. 2017 Apr 14;17(1):71. Available from: http://dx.doi.org/10.1186/s12883-017-0852-z.
40. Martins FPA, Massetti T, Crocetta TB, Lopes PB, da Silva AA, Figueiredo EF, et al. Analysis of motor performance in individuals with cerebral palsy using a non-immersive virtual reality task - a pilot study. Neuropsychiatr Dis Treat [Internet]. 2019 Feb 4;15:417–28. Available from: http://dx.doi.org/10.2147/NDT.S184510.
41. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol [Internet]. 2017 Sep;128(9):1774–809. Available from: http://dx.doi.org/10.1016/j.clinph.2017.06.001.
42. Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, et al. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov Disord [Internet]. 2006 Oct;21(10):1693–702. Available from: http://dx.doi.org/10.1002/mds.21012.
43. Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain?: tDCS-induced changes of rCBF. Eur J Neurosci [Internet]. 2005 Jul;22(2):495–504. Available from: http://dx.doi.org/10.1111/j.1460-9568.2005.04233.x.
44. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson's disease. Neurosci Lett [Internet]. 2014 Oct 17;582:27–31. Available from: http://dx.doi.org/10.1016/j.neulet.2014.08.043.

45. Proud EL, Miller KJ, Bilney B, Balachandran S, McGinley JL, Morris ME. Evaluation of measures of upper limb functioning and disability in people with Parkinson disease: a systematic review. Arch Phys Med Rehabil [Internet]. 2015 Mar;96(3):540–51.e1. Available from: http://dx.doi.org/10.1016/j.apmr.2014.09.016.

46. Zettergren K. The effects of Nintendo Wii Fit training on gait speed, balance, functional mobility and depression in one person with Parkinson's disease. Medical and Health Science Journal [Internet]. 2011;9:18–25. Available from: https://go.gale.com/ps/i.do?id=GALE%7CA272510771&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=18041884&p=HRCA&sw=w.

47. Palacios-Navarro G, Albiol-Pérez S, García-Magariño I. A Kinect-based virtual reality system for Parkinson disease rehabilitation. In: New Contributions in Information Systems and Technologies [Internet]. Cham: Springer International Publishing; 2015. p. 1133–9. (Advances in intelligent systems and computing). Available from: http://dx.doi.org/10.1007/978-3-319-16486-1_112.

48. Esculier JF, Vaudrin J, Bériault P, Gagnon K, Tremblay LE. Home-based balance training programme using Wii Fit with balance board for Parkinsons's disease: a pilot study. J Rehabil Med [Internet]. 2012 Feb;44(2):144–50. Available from: http://dx.doi.org/10.2340/16501977-0922.

49. Shen X, Wong-Yu ISK, Mak MKY. Effects of exercise on falls, balance, and gait ability in Parkinson's disease: A meta-analysis: A meta-analysis. Neurorehabil Neural Repair [Internet]. 2016 Jul;30(6):512–27. Available from: http://dx.doi.org/10.1177/1545968315613447.

50. Pompeu JE, Mendes FADS, Silva KG da, Lobo AM, Oliveira T de P, Zomignani AP, et al. Effect of Nintendo WiiTM-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial. Physiotherapy [Internet]. 2012 Sep;98(3):196–204. Available from: http://dx.doi.org/10.1016/j.physio.2012.06.004.

51. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? J Gerontol A Biol Sci Med Sci [Internet]. 2011 Feb;66(2):234–40. Available from: http://dx.doi.org/10.1093/gerona/glq201.

52. Lee NY, Lee DK, Song HS. Effect of virtual reality dance exercise on the balance, activities of daily living, and depressive disorder status of Parkinson's disease patients. J Phys Ther Sci [Internet]. 2015 Jan;27(1):145–7. Available from: http://dx.doi.org/10.1589/jpts.27.145.

53. Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D, et al. Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation: a pilot randomized clinical trial and proof of principle: A pilot randomized clinical trial and proof of principle. Stroke [Internet]. 2010 Jul;41(7):1477–84. Available from: http://dx.doi.org/10.1161/STROKEAHA.110.584979.

54. Canning CG, Allen NE, Nackaerts E, Paul SS, Nieuwboer A, Gilat M. Virtual reality in research and rehabilitation of gait and balance in Parkinson disease. Nat Rev Neurol [Internet]. 2020 Aug;16(8):409–25. Available from: http://dx.doi.org/10.1038/s41582-020-0370-2.

55. De Keersmaecker E, Lefeber N, Geys M, Jespers E, Kerckhofs E, Swinnen E. Virtual reality during gait training: does it improve gait function in persons with central nervous system movement disorders? A systematic review and meta-analysis. NeuroRehabilitation [Internet]. 2019;44(1):43–66. Available from: http://dx.doi.org/10.3233/NRE-182551.

56. Shafer RL, Solomon EM, Newell KM, Lewis MH, Bodfish JW. Visual feedback during motor performance is associated with increased complexity and adaptability of motor and neural output. Behav Brain Res [Internet]. 2019 Dec 30;376(112214):112214. Available from: http://dx.doi.org/10.1016/j.bbr.2019.112214.

57. Villiger M, Bohli D, Kiper D, Pyk P, Spillmann J, Meilick B, et al. Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. Neurorehabil Neural Repair [Internet]. 2013 Oct;27(8):675–83. Available from: http://dx.doi.org/10.1177/1545968313490999.

58. O'Brien J, Roberts D, Monaghan K. Virtual reality to improve motor function after stroke: Past, present, and future. Physiother Pract Res [Internet]. 2019 Sep 13 [cited 2025 Sep 19];40(2):113–6. Available from: https://pure.atu.ie/en/publications/virtual-reality-to-improve-motor-function-after-stroke-past-prese-3.

59. Petersen K, Van Wouwe N, Stark A, Lin YC, Kang H, Trujillo-Diaz P, et al. Ventral striatal network connectivity reflects reward learning and behavior in patients with Parkinson's disease. Hum Brain Mapp [Internet]. 2018 Jan;39(1):509–21. Available from: http://dx.doi.org/10.1002/hbm.23860.

60. Shen X, Mak MKY. Balance and gait training with augmented feedback improves balance confidence in people with Parkinson's disease: A randomized controlled trial: A randomized controlled trial. Neurorehabil Neural Repair [Internet]. 2014 Jul;28(6):524–35. Available from: http://dx.doi.org/10.1177/1545968313517752.

61. Sihvonen AJ, Särkämö T, Leo V, Tervaniemi M, Altenmüller E, Soinila S. Music-based interventions in

neurological rehabilitation. Lancet Neurol [Internet]. 2017 Aug;16(8):648–60. Available from: http://dx.doi.org/10.1016/S1474-4422(17)30168-0.

62. Wan CY, Schlaug G. Music making as a tool for promoting brain plasticity across the life span. Neuroscientist [Internet]. 2010 Oct;16(5):566–77. Available from: http://dx.doi.org/10.1177/1073858410377805.
63. Schlaug G. Musicians and music making as a model for the study of brain plasticity. Prog Brain Res [Internet]. 2015 Feb 11;217:37–55. Available from: http://dx.doi.org/10.1016/bs.pbr.2014.11.020.
64. Vaquero L, Hartmann K, Ripollés P, Rojo N, Sierpowska J, François C, et al. Structural neuroplasticity in expert pianists depends on the age of musical training onset. Neuroimage [Internet]. 2016 Feb 1;126:106–19. Available from: http://dx.doi.org/10.1016/j.neuroimage.2015.11.008.
65. Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev [Internet]. 2017 Nov 20;11(1):CD008349. Available from: http://dx.doi.org/10.1002/14651858.CD008349.pub4.
66. Liu X, Liu H, Liu Z, Rao J, Wang J, Wang P, et al. Transcranial direct current stimulation for Parkinson's disease: A systematic review and meta-analysis. Front Aging Neurosci [Internet]. 2021 Oct 28;13:746797. Available from: http://dx.doi.org/10.3389/fnagi.2021.746797.
67. Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. Mol Psychiatry [Internet]. 2020 Feb;25(2):397–407. Available from: http://dx.doi.org/10.1038/s41380-019-0499-9.
68. Nascimento LR, Nakamura-Palacios EM, Boening A, Cordeiro BNL, Cabral DL, Swarowsky A, et al. Transcranial direct current stimulation (tDCS) in addition to walking training on walking, mobility, and reduction of falls in Parkinson's disease: study protocol for a randomized clinical trial. Trials [Internet]. 2021 Sep 21;22(1):647. Available from: http://dx.doi.org/10.1186/s13063-021-05603-z.
69. Yavari F, Jamil A, Mosayebi Samani M, Vidor LP, Nitsche MA. Basic and functional effects of transcranial Electrical Stimulation (tES)-An introduction. Neurosci Biobehav Rev [Internet]. 2018 Feb;85:81–92. Available from: http://dx.doi.org/10.1016/j.neubiorev.2017.06.015.
70. Simonsmeier BA, Grabner RH, Hein J, Krenz U, Schneider M. Electrical brain stimulation (tES) improves learning more than performance: A meta-analysis. Neurosci Biobehav Rev [Internet]. 2018 Jan;84:171–81. Available from: http://dx.doi.org/10.1016/j.neubiorev.2017.11.001.
71. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. Parkinsonism Relat Disord [Internet]. 2009 Dec;15 Suppl 3:S53–8. Available from: http://dx.doi.org/10.1016/S1353-8020(09)70781-3.
72. Broeder S, Nackaerts E, Heremans E, Vervoort G, Meesen R, Verheyden G, et al. Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. Neurosci Biobehav Rev [Internet]. 2015 Oct;57:105–17. Available from: http://dx.doi.org/10.1016/j.neubiorev.2015.08.010.
73. Hsieh YW, Lin KC, Horng YS, Wu CY, Wu TC, Ku FL. Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: a randomized controlled trial. J Neurol [Internet]. 2014 May;261(5):1037–45. Available from: http://dx.doi.org/10.1007/s00415-014-7345-4.
74. Ang KK, Guan C, Phua KS, Wang C, Zhao L, Teo WP, et al. Facilitating effects of transcranial direct current stimulation on motor imagery brain-computer interface with robotic feedback for stroke rehabilitation. Arch Phys Med Rehabil [Internet]. 2015 Mar;96(3 Suppl):S79–87. Available from: http://dx.doi.org/10.1016/j.apmr.2014.08.008.
75. Teo WP, Muthalib M, Yamin S, Hendy AM, Bramstedt K, Kotsopoulos E, et al. Does a combination of virtual reality, neuromodulation and neuroimaging provide a comprehensive platform for neurorehabilitation? - A narrative review of the literature. Front Hum Neurosci [Internet]. 2016 Jun 24;10:284. Available from: http://dx.doi.org/10.3389/fnhum.2016.00284.
76. Harris DM, Rantalainen T, Muthalib M, Johnson L, Duckham RL, Smith ST, et al. Concurrent exergaming and transcranial direct current stimulation to improve balance in people with Parkinson's disease: study protocol for a randomised controlled trial. Trials [Internet]. 2018 Jul 16;19(1):387. Available from: http://dx.doi.org/10.1186/s13063-018-2773-6.
77. Correa TV, da Silva Rocha Paz T, Allodi S, de Britto VLS, Correa CL. Progressive muscle-strength protocol for the functionality of upper limbs and quality of life in individuals with Parkinson's disease: Pilot study. Complement Ther Med [Internet]. 2020 Aug;52(102432):102432. Available from: http://dx.doi.org/10.1016/j.ctim.2020.102432.
78. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. Neurorehabil Neural Repair [Internet]. 2009 Jul;23(6):600–8. Available from: http://

dx.doi.org/10.1177/1545968308328726.

79. Jansen AE, Koop MM, Rosenfeldt AB, Alberts JL. High intensity aerobic exercise improves bimanual coordination of grasping forces in Parkinson's disease. Parkinsonism Relat Disord [Internet]. 2021 Jun;87:13–9. Available from: http://dx.doi.org/10.1016/j.parkreldis.2021.04.005.
80. Shah C, Beall EB, Frankemolle AMM, Penko A, Phillips MD, Lowe MJ, et al. Exercise therapy for Parkinson's disease: Pedaling rate is related to changes in motor connectivity. Brain Connect [Internet]. 2016 Feb;6(1):25–36. Available from: http://dx.doi.org/10.1089/brain.2014.0328.
81. Chuang CS, Chen YW, Zeng BY, Hung CM, Tu YK, Tai YC, et al. Effects of modern technology (exergame and virtual reality) assisted rehabilitation vs conventional rehabilitation in patients with Parkinson's disease: a network meta-analysis of randomised controlled trials. Physiotherapy [Internet]. 2022 Dec;117:35–42. Available from: http://dx.doi.org/10.1016/j.physio.2022.07.001.
82. Moraes ÍAP, Lima JA, Silva NM, Simcsik AO, Silveira AC, Menezes LDC, et al. Effect of longitudinal practice in real and virtual environments on motor performance, physical activity and enjoyment in people with autism spectrum disorder: A prospective randomized crossover controlled trial. Int J Environ Res Public Health [Internet]. 2022 Nov 8;19(22):14668. Available from: http://dx.doi.org/10.3390/ijerph192214668.

Resumo

Introdução: a Doença de Parkinson é um distúrbio neurológico progressivo resultante da morte de células produtoras de dopamina na substância negra. Pessoas com Doença de Parkinson necessitam de terapias de reabilitação eficazes para controlar os sintomas motores comumente associados a essa condição. A estimulação transcraniana por corrente contínua (ETCC) é uma ferramenta promissora para aprimorar o funcionamento sensório-motor em pessoas com Parkinson, e a combinação dessa técnica com tarefas de Realidade Virtual (RV) vem sendo explorada no campo do desempenho motor. No entanto, ainda há escassez de evidências sobre essa associação.

Objetivo: comparar o desempenho motor entre uma sessão única ativa ou simulada de estimulação transcraniana por corrente contínua combinada com uma tarefa em Realidade Virtual em indivíduos com Doença de Parkinson.

Método: foi conduzido um protocolo de ensaio clínico randomizado, triplo-cego. Cinquenta e quatro indivíduos, com pontuação entre 1 e 4 na Escala Modificada de Hoehn & Yahr, foram recrutados. Os participantes foram aleatoriamente distribuídos nos seguintes grupos: ETCC ativa (ETCC + tarefa em RV) ou ETCC simulada (sham ETCC + tarefa em RV). O protocolo teve duração de 18 minutos, composto pelos seguintes blocos: 5 minutos de estímulo em repouso inicial, 4 minutos de ETCC + tarefa em RV para os membros superiores, 4 minutos de ETCC + tarefa em RV para os membros inferiores e 5 minutos de estímulo em repouso final. O protocolo ativo de ETCC utilizou baixa frequência, com intensidade de 2 miliamperes (mA), aplicada sobre o córtex motor primário (M1) do lado dominante do cérebro.

Resultados: foi observado um efeito significativo entre Grupos e Blocos nas medidas de erro absoluto e erro variável. Ambos os grupos, ativo e simulado, apresentaram melhora no desempenho dos membros superiores em comparação com os membros inferiores.

Conclusão: a ETCC ativa pode ser uma ferramenta eficaz para aprimorar o desempenho motor durante uma tarefa em Realidade Virtual. Isso pode envolver melhorias na precisão e na exatidão dos movimentos dos membros superiores e inferiores em indivíduos com Doença de Parkinson. Efeitos positivos foram observados no grupo ativo mesmo após uma única sessão de ETCC. Pesquisas futuras são recomendadas para investigar os efeitos de protocolos de longa duração, incluindo medidas de acompanhamento.

Keywords: Doença de Parkinson, ETCC, Realidade Virtual.