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TDCS for parkinson‘s disease disease-related pain: A randomized trial

Yeray González-Zamorano [a,b,c,d], Francisco José Sánchez-Cuesta [d,e], Marcos Moreno-Verdú [d,e], Aida Arroyo-Ferrer [d,e], Josué Fernández-Carnero [b,c,*], K. Ray Chaudhuri [f,g], Anna Fieldwalker [f], Juan Pablo Romero [c,d,e,h]

[a] International Doctorate School, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, 28933 Alcorcón, Spain
[b] Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Rey Juan Carlos University, 28933 Alcorcón, Spain
[c] Cognitive Neuroscience, Pain and Rehabilitation Research Group (NECODOR), Faculty of Health Sciences, Rey Juan Carlos University, Madrid, Spain
[d] Brain Injury and Movement Disorders Neurorehabilitation Group (GINDAT), Institute of Life Sciences, Francisco de Vitoria University, Pozuelo de Alarcón, Spain
[e] Faculty of Experimental Sciences, Francisco de Vitoria University, 28223 Pozuelo de Alarcón, Spain
[f] Department of Basic and Clinical Neurosciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[g] Parkinson's Foundation Centre of Excellence, King's College Hospital, London, United Kingdom
[h] Brain Damage Unit, Beata María Ana Hospital, 28007 Madrid, Spain

HIGHLIGHTS

- First trial using tDCS for Parkinsońs disease-related pain has been performed.
- tDCS alleviates perceived pain and increases descending inhibitory systems in Parkinsońs disease patients.
- Conditioned Pain Modulation could mediate pain relief in Parkinsońs disease.

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ABSTRACT

Objective: To evaluate the effects of transcranial direct current stimulation (tDCS) on Parkinson's disease (PD)-related pain.
Methods: This triple-blind randomized controlled trial included twenty-two patients (age range 38–85, 10 male) with PD-related pain. Eleven subjects received ten sessions of 20 minutes tDCS over the primary motor cortex contralateral to pain at 2 mA intensity. Eleven subjects received sham stimulation. Outcome measures included changes in the Kińgs Parkinsońs Pain Scale (KPPS), Brief Pain Inventory (BPI), widespread mechanical hyperalgesia (WMH), temporal summation of pain (TS), and conditioned pain modulation (CPM).
Results: Significant differences were found in KPPS between groups favoring the active-tDCS group compared to the sham-tDCS group at 15-days follow-up ($p = 0.014$) but not at 2 days post-intervention ($p = 0.059$). The active-group showed significant improvements over the sham-group after 15 days ($p = 0.017$). Significant changes were found in CPM between groups in favor of active-tDCS group at 2 days post-intervention ($p = 0.002$) and at 15 days ($p = 0.017$). No meaningful differences were observed in BPI or TS.
Conclusions: tDCS of the primary motor cortex alleviates perceived PD-related pain, reduces pain sensitization, and enhances descending pain inhibition.
Significance: This is the first study to test and demonstrate the use of tDCS for improving PD-related pain.

Abbreviations: BDI, Becḱs Depression Inventory; BPI, Brief Pain Inventory; CPM, Conditioned Pain Modulation; IMMPACT, Initiative on Methods, Measurement and Pain Assessment in Clinical Trials; KPPS, Kińgs Parkinsońs Disease Pain Scale; M1, Primary Motor Cortex; MMSE, Mini-Mental State Examination; PCS, Pain Catastrophizing Scale; PDPCS, Parkinson's Disease Pain Classification System; PPT, Pain Pressure Thresholds; STAI, State-Trait Anxiety Inventory; tDCS, transcranial Direct Current Stimulation; TS, Temporal Summation; TSK-11, Tampa Scale for Kinesiophobia; UPDRS, Unified Parkinson's disease Rating Scale; VNPRS, Verbal Numeric Pain Rating Scale; WMH, Widespread Mechanical Hyperalgesia.

* Corresponding author at: Atenas Avenue s/n. Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Rey Juan Carlos University, 28933 Alcorcón, Spain.

E-mail addresses: yeray.gonzalez@urjc.es (Y. González-Zamorano), fjose.sanchez@ufv.es (F. José Sánchez-Cuesta), aida.ferrer@ufv.es (A. Arroyo-Ferrer), josue.fernandez@urjc.es (J. Fernández-Carnero), ray.chaudhuri@kcl.ac.uk (K.R. Chaudhuri), anna.fielding@kcl.ac.uk (A. Fieldwalker), p.romero.prof@ufv.es (J.P. Romero).

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1. Introduction

Pain affects between 40 to 85% of Parkinson's disease (PD) patients (Broen et al., 2012; Rana et al., 2013; Silverdale et al., 2018) and impacts severely their quality of life (Martinez-Martin et al., 2011). However, paradoxically, it remains an under-reported symptom (Chaudhuri and Schapira, 2009), leading to its consequent under-treatment.

Various taxonomies have been used to classify PD-related pain. On the one hand, the Parkinsońs Disease Pain Classification System (PDPCS) recognize three descriptors: nociceptive, neuropathic and nociplastic. On the other hand, Kińgs Parkinsońs Pain Scale identify several more: musculoskeletal, chronic central or visceral, related to "on-off" fluctuations, dyskinetic-dystonic, nocturnal due to immobility or restless legs syndrome, orofacial, from inflammation or edema, and radicular pain. However, there is no consensus about what classification better describes PD-related pain. Besides, they barely consider the pathophysiological mechanisms (Blanchet and Brefel-Courbon, 2018) that allow us to identify the etiology and pathogenesis of pain, which is considered crucial for proposing a coherent treatment. Generally, it appears that PD patients might experience changes in peripheral transmission, sensory-discriminative processing, and the perception and interpretation of pain across various levels, due to neurodegeneration in dopaminergic pathways, and non-dopaminergic structures involved in pain processing (Gandolfi et al., 2017). This dysregulation of the dopaminergic system can impact the pain experience both directly, by enhancing nociceptive signals, and indirectly, influencing expectations and interpretation of nociceptive information (Jarcho et al., 2012). This could also lead to alteration in psychophysical pain processing features (Chen et al., 2015; Granovsky et al., 2013; Perrotta et al., 2011). Therefore, it is hypothesized that central mechanisms play a key role in the onset and persistence of pain in PD patients (Antonini et al., 2018). Indeed, PD pain subtype has been described (Sauerbier et al., 2016).

There is no clear efficacy of dopaminergic drugs for improving neither pain sensitivity nor endogenous pain modulation systems (Chen et al., 2015; Gerdelat-Mas et al., 2007; Granovsky et al., 2013). In fact, there is a shortage of non-pharmacological management protocols for PD-related pain (Karnik et al., 2020).

Non-invasive neuromodulation approaches using transcranial direct current stimulation (tDCS) have been successfully used to activate or inhibit different cortical areas. Interestingly, reduced cortical excitability is a frequent occurrence not only in patients with pain (Burns et al., 2016) but also in those with PD (Chen and Chen, 2019; Tremblay and Tremblay, 2002). Indeed, different therapies have been developed to counteract this cortical excitability reduction and thereby obtaining effective pain relief. It is hypothesized that tDCS over the primary motor cortex (M1) may alleviate pain, among other mechanisms, by enhancing excitability in the stimulated region as well as in other areas involved in pain processing, including sensory and emotional aspects. This includes structures like the thalamus, dorsolateral prefrontal cortex, cingulate cortex, insula, and brainstem (Dasilva et al., 2012; Lefaucheur, 2006), due to the connectivity between the cortex and subcortex (Lang et al., 2005). These increments have been linked with analgesic effects in comparable chronic pain conditions (Conde-Antón et al., 2020; Feng et al., 2019; Fregni et al., 2021; Hsu et al., 2021; Pacheco-Barrios et al., 2020; Ramger et al., 2019; Zhang et al., 2021).

M1 might be an effective focus for therapeutic brain neuromodulation in PD. Strikingly, there are no clinical trials that aim to target cortical excitability to treat PD-related pain.

The main objective was to assess the effects of tDCS over M1 on clinical perceived PD-related pain. Secondarily, we assessed the effects of tDCS over M1 on general pain, interference of pain, and psychophysical pain processing features in PD patients.

2. Materials and methods

The CONSORT reporting guidelines has been followed to ensure the quality of the manuscript (Schulz et al., 2010).

2.1. Study design and participants

This study was a triple-blinded randomized placebo-controlled trial with a parallel design. Patients with idiopathic PD, diagnosed based on the United Kingdom PD Society Brain Bank criteria and experiencing PD-related otherwise unexplained pain, were enrolled in a PD outpatient's clinic in Madrid, by the lead investigator (YGZ). PD-related pain was determined by step one of the PDPCS (Mylius et al., 2020), involving four queries: whether pain severity increased post-onset of PD symptoms, if the pain intensified alongside motor symptoms, if the pain was associated to dyskinesia, and whether pain relief occurred upon taking PD medication. If one of the four questions was affirmative, PD-related pain was assumed. As there is research indicating that female gender tends to experience higher pain sensitivity (Chesterton et al., 2003), the study ensured the inclusion of at least one third female participants. Specific inclusion and exclusion criteria are those related to the study's published protocol (González-Zamorano et al., 2021) and are listed in Table 1. Informed consent, approved by the Institutional Review Boards (IRB) (internal identifier 20–515), was obtained from all patients, following the principles of the Declaration of Helsinki. The trial was registered at https://www.clinicaltrials.gov (NCT04651699).

Table 1
Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
Older than 18.	History of neurologic disease different from Parkinson's disease.
Neuroimaging study without previous pathologies.	Presence of pain non-related to Parkinson's disease.
Score > 5 in transfers (bed to chair and back) item in Barthel Index.	Dermatologic problems, wounds, or ulcers in the electrode's application area.
Score $\geq$ 24 in Mini-Mental State Examination.	Presence of implants or metal pieces in the head.
Tolerability for the application of electrotherapy.	Presence of cardiac pacemaker, vagal, brain or transcutaneous stimulators, medication pumps, ventriculoperitoneal shunts or aneurysm clips.
Able to provide informed consent to participate in the study.	Significative difficulties in language.
	History of alcohol or drugs abuse.
	Non-controlled medical problems.
	Pregnancy.
	Epilepsy.

2.2. Randomization and masking

Randomization was conducted using GraphPad software (GraphPad Software, San Diego, C.A., U.S.A.), by an independent investigator. Participants were randomly divided into two groups: active-tDCS (ac-tDCS) or sham-tDCS (s-tDCS). To ensure triple-blind condition, both groups had identical electrode placements, and the "double-blind" feature of the StarstimtDCS® Software (Neuroelectrics Inc, Barcelona, Spain) was used to hide the protocol by entering a non-specific code. The investigator responsible for concealing allocation (AAF) placed the group codes in sealed envelopes which were then opened by the therapist (FJS) at the intervention time ignoring which code corresponded with each intervention. Both the evaluator (YGZ) and the statistician (JFC) were kept unaware using the same neutral codes. To evaluate the effectiveness of the blinding, patients were queried about which type of stimulation they believed they had received.

2.3. Procedures

All participants underwent 10 consecutive daily sessions either ac-tDCS or s-tDCS for two weeks (from Monday to Friday) 1–2 hours after medication intake (Mena et al., 2009) to ensure ON state. Along with the intervention procedure, patients did not receive any other active treatment. Throughout the interventions, each participant was seated comfortably (Brunoni et al., 2011). Potential adverse effects were evaluated after every session by the Comfort Rating Questionnaire (Palm et al., 2014; Poreisz et al., 2007). The security and replicability recommendations were followed strictly (Woods et al., 2016).

2.4. Active transcranial direct current stimulation

Direct current was delivered using StarstimtDCS® stimulator using saline-soak pair of surface sponge electrodes (35 cm2). The anode electrode was placed over C3 or C4 (EEG 10/20 international system) and the cathode over the contralateral supraorbital area (Fp2 or Fp1, respectively), for stimulating the M1 contralateral to pain (Lefaucheur et al., 2004; Nitsche and Paulus, 2001). For patients experiencing bilateral pain, the left hemisphere was selected as the target because of the broad changes tDCS induces in contralateral cortical areas (Lang et al., 2005). A steady current of 2 mA intensity (subthreshold intensity) was administered for 20 min (Fregni et al., 2006), including a ramp-up period of 30 seconds and a ramp-down period of the same duration.

2.5. Sham transcranial direct current stimulation

Electrodes were positioned identically to those used for active stimulation. However, after the initial 30 seconds ramping active current, the stimulator turned off so. This allowed subjects to experience the initial itching sensation, but no current was elicited for the rest of the stimulation period. This approach of sham stimulation has proven reliable for blinding subjects. (Gandiga et al., 2006).

2.6. Outcome measures

The outcome measures adhered to the guidelines set by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) guidelines (Dworkin et al., 2005).

A trained physical therapist assessed all patients at three time points: before treatment (baseline), 2 days after finishing the 10 sessions (post-intervention), and 15 days after the end of the treatment (follow-up). Every participants underwent evaluation 1 to 2 h after consuming their dopaminergic medication (Mena et al., 2009), to ensure ON state.

2.6.1. Baseline outcome measures

Emotional and cognitive functioning were assessed at baseline. Depressive symptoms, anxiety, fear of movement-related pain, and catastrophizing thinking were measured by the Spanish versions of Becḱs Depression Inventory (BDI) (Wiebe and Penley, 2005), State-Trait Anxiety Inventory (STAI) (Spielberger and et al, 1971), Tampa Scale for Kinesiophobia (TSK-11) (Gómez-Pérez et al., 2011), and Pain Catastrophizing Scale (PCS) (García Campayo et al., 2008), respectively.

2.6.2. Main outcome measure

2.6.2.1. Kingś Parkinsoń s pain Scale (KPPS). PD-related pain was assessed by the KPPS (Chaudhuri et al., 2015; Perez-Lloret et al., 2016). It consists of 14 items covering 7 pain domains: Musculoskeletal; Chronic; Fluctuation-related; Nocturnal; Oro-facial; Discoloration, Oedema/Swelling; Radicular. Each item is rated based on severity (0, none to 3, very severe) multiplied by frequency (0, never to 4, all the time) yielding a subscore ranging from 0 to 12. The total score is the sum of these subscores and can range from 0 to 168 points. The KPPS appears to be a valid and reliable scale to assess different types of pain in PD (Cronbach́s alpha = 0.78). The KPPS is recognized as a valid and reliable scale for measuring outcomes (Chaudhuri et al., 2015).

2.6.3. Secondary outcomes

2.6.3.1. Brief pain Inventory (BPI). Pain intensity and its interference on the function and welfare of patients was measured by the Spanish BPI short form. Patients were asked to rate different intensities of their pain in the previous 24 hours and the interference with activities of daily living, social functioning and emotional status (Cleeland and Ryan, 1994). Pain and interference scales of the Spanish BPI short form are considered valid and reliable (Cronbach's alpha = 0.931) (de Andrés et al., 2015). Its short form has been deemed "recommended with caution" for the evaluation of pain in PD patients, which means that it is recommended because it meets the majority of criteria but has not been yet validated in PD (Perez-Lloret et al., 2016).

2.6.3.2. Widespread mechanical hyperalgesia (WMH). To evaluate WMH, Pain Pressure Thresholds (PPTs) were assessed in two locations with a handheld pressure algometer (FPX Model, Wagner Instruments, Greenwich, CT, USA). One PPT was taken over the location of greatest pain (peripheral hyperalgesia), and the other was measured on the middle of the distal phalanx of the thumb (central hyperalgesia). The PPTs were determined by applying the algometer perpendicular to the skin increasing at a rate of 1 kg/s (Chesterton et al., 2003) until pain was first felt. Three measures were taken in each location with 30-seconds rest between them, recording the average as the final PPT. WMH was then calculated by adding both final PPT́s (Rolke et al., 2006), with lower values of WMH indicating more pronounced pain expansion. The reliability of algometry in assessing the PPT has been shown to be good to excellent, evidenced by an intraclass correlation coefficient ranging from 0.84 to 0.96 (Bisset et al., 2015).

2.6.3.3. Temporal Summation (TS). The TS phenomenon was induced by applying 10 pulses from the handheld pressure algometer to the middle of the distal phalanx of the left thumb with the intensity of the PPT. The intensity for each pulse was set to the previously calculated PPT (Ferrer-Peña et al., 2019). The pressure intensity increased at a rate of 2 kg/s until reaching the previously determined PPT intensity in each pulse, with a one-second interval between stimuli (Graven-Nielsen et al.,

2015; Nie et al., 2005). Prior to the first pulse, subjects were instructed on using a verbal numeric pain rating scale (VNPRS), which spans from 0 (“no pain”) to 10 (“the worst possible pain”) (Kliger et al., 2015). They were then asked to rate the pain intensity of both the 1st and 10th pressure pulses. To obtain the final TS score, the VNPRS value of the 1st pulse was subtracted to the VNPRS value of the 10tf pulse. This protocol is the optimal method reported for inducing TS with pressure pain (Nie et al., 2005) and its sensitivity and reliability is comparable with other procedures such as computer-controlled cuff algometry (Graven-Nielsen et al., 2015).

2.6.3.4. Conditioned pain modulation (CPM). The CPM task was scheduled 5 minutes apart from the Temporal Summation (TS) task to avoid any interference. The procedure began with measuring one PPT on the middle of the distal phalanx of the right thumb using the previously mentioned handheld algometer (test stimulus). Afterwards, patients were asked to submerge their opposite hand up to the wrist in stirred ice-cold water (0–4 ∘C) for 3 minutes (conditioning stimulus)**.** This immersion aimed to induce moderate to severe pain, thereby activating the descending pain modulatory system. Should the pain become intolerable before the completion of the three-minute period, patients had the option to remove their hand. Each patient had to confirm verbally that a moderate-severe pain was reached. Right after the hand was removed, a second PPT measure was taken in the same location as the first one (conditioned stimulus). The combination of PPT induced by handheld pressure algometer as test stimulus and cold water as conditioning stimulus are considered to be the most reliable method to assess CPM (Imai et al., 2016; Olesen et al., 2012).

2.6.3.5. Statistical analyses. To calculate the sample size, we first conducted a pilot study with 9 patients per group (Supplementary Table 2) to obtain the effect size of the main variable, the KPPS (Cohen's d = 0.45) (Supplementary Table 3). Using G*Power software (version 3.1, Heinrich Heine Universität, Germany), we then calculated the required sample size using a two-factor ANOVA with 2 groups and 3 measurements. Considering an alpha level of 0.05 and a power of 95%, a correlation among repeated measures of 0.40 and non-sphericity correction of 1, a minimal recruitment of 18 participants was required, but considering a dropout rate of 20%, a total of 22 participants were included.

For statistical analysis, the SPSS version 25.0 for Windows (IBM Corp. Armonk, NY) was used. Alpha was set to 0.05 for statistical significance. All analyses were conducted with 95% confidence intervals. The Shapiro-Wilk test was applied to detect significant deviations from normality (P > 0.05), and all variables showed a normal distribution. Between-group differences at baseline were analyzed using the two-samples t-test and chi-square test for continuous and dichotomous variables respectively.

For hypothesis testing, a two-factor ANOVA was conducted with the within-subject factor time with 3 levels (pre, post and follow-up) and the between-subject factor group with 2 levels (ac-tDCS and s-tDCS). *Post-hoc* analysis was performed with Bonferroni correction for multiple comparisons. The effect size for each pairwise comparison was calculated as Cohen's d, and interpreted as small, medium, or large if d was 0.20–0.49, 0.50–0.79 and > 0.8 respectively. Sensitivity analysis was performed using analysis of covariance (ANCOVA) with any variables showing statistically significant between-group differences at baseline as covariates.

The appropriateness of patient blinding was evaluated by comparing the accuracy of patients' responses about the type of stimulation received (active or sham) between groups using the chi-square test.

2.7. Data availability

The data that support the findings are freely available on the Open Science Framework at https://osf.io/u5mys/.

3. Results

3.1. Participant flow

Thirty-five patients were initially assessed for eligibility from May 2021 to June 2022, but eleven were ineligible for several reasons outlined in Fig. 1. Thus, 22 participants met the eligibility criteria and were enrolled and randomized to receive real stimulation (n = 11) or sham (n = 11), respectively. Two patients dropped out because of reasons not related to study procedures, one of them the day before the first treatment session, and the other after the third one. Therefore, two more patients were enrolled and randomized (Fig. 1). A total sample of 22 patients was finally analysed by original assigned groups (11 per group) by January 2023, as it was previously calculated.

3.2. Baseline characteristics of participants

Demographic and clinical characteristics at baseline are reported in Table 2. After randomization, the groups did not exhibit statistically significant differences in any of the baseline variables, except for levodopa equivalent daily dose (LEDD) ($t_{(20)}$ = 2.58; P = 0.02). Therefore, sensitivity analyses were performed with baseline LEDD as covariate.

3.2.1. Kińgs Parkinsońs disease pain Scale (KPPS) overall score

For the KPPS overall score, the ANOVA showed a significant effect for time ($F_{(2,40)}$ = 11.506; P < 0.001) and group and time interaction ($F_{(2,40)}$ = 12.738;P < 0.001) (Fig. 2a;Table 3). *Post-hoc* analysis showed significant within-group pre-, post and follow-up differences only for the ac-tDCS group (P < 0.001; Table 3). Between-group differences in favor of ac-tDCS group at follow-up were found (P = 0.014) with a large effect size (d = 1.14) but not immediately after the treatment (P = 0.059).

3.2.2. King's Parkinson's disease pain Scale (KPPS) domain scores

The ANOVA did not show a significant effect for time or an interaction between group and time for changes in domains 1 (musculoskeletal pain), 2 (chronic pain), 5 (oro-facial pain) and 7 (radicular pain) (all P > 0.05).

However, the ANOVA showed effects for domains 3 (fluctuation-related pain), 4 (nocturnal pain) and 6 (discoloration/oedema/swelling). A statistically significant interaction between group and time ($F_{(2, 40)}$ = 7.158; P = 0.009) for changes in domain 3 (Fig. 2b; Table 3) was found. *Post-hoc* analysis revealed significant within-group differences between pre- and follow-up in favor of the ac-tDCS group (P = 0.002). *Post-hoc* analyses demonstrated significant differences between groups in favor of ac-tDCS group at follow-up (P = 0.004) with a large effect size (d = 1.38) but not immediately after the treatment (P = 0.214).

The ANOVA showed a significant effect for time ($F_{(2,40)}$ = 6.069; P < 0.01) and statistically significant interaction between group and time ($F_{(2,40)}$ = 6.566; P < 0.01) for changes in domain 4 (Fig. 2c; Table 3). *Post-hoc* analysis revealed meaningful within-group differences in group ac-tDCS between pre- and post-intervention (P < 0.001) and between pre- and follow-up (P < 0.01). No between-group differences were found (P > 0.05).

The ANOVA showed a significant effect for time ($F_{(2,40)}$ = 4,167; P = 0.02) and statistically significant interaction between group and time ($F_{(2,40)}$ = 11.443; P < 0.001) for changes in domain 6

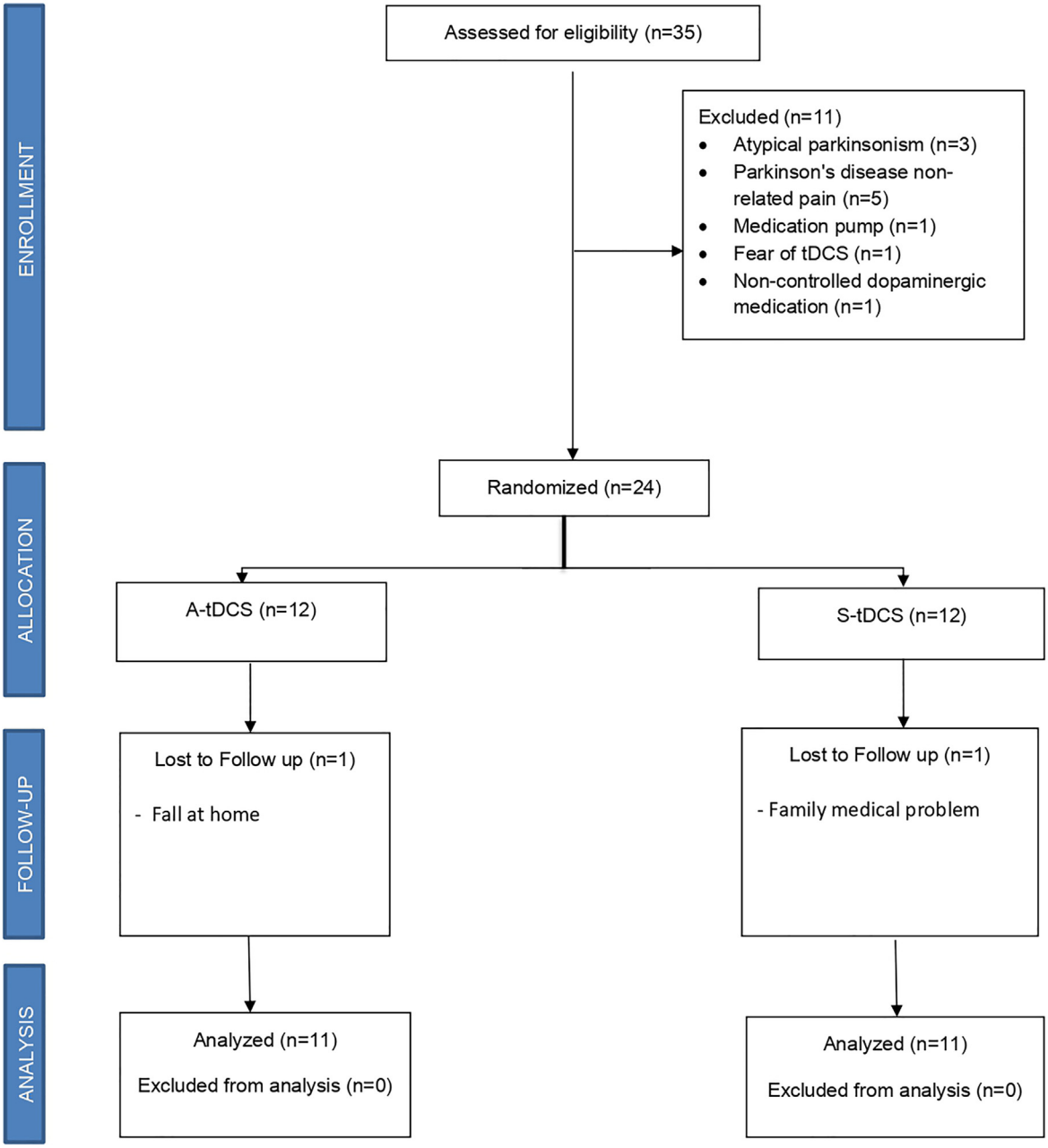

Fig. 1. Flowchart of study participants according to CONSORT 2010. Legend. tDCS: transcranial direct current stimulation; A-tDCS: active transcranial direct current stimulation; S-tDCS: sham transcranial direct current stimulation.

(Fig. 2d; Table 3). *Post-hoc* analysis revealed significant within-group differences only for the ac-tDCS group between pre- and post-intervention (P < 0.001) and between pre- and follow-up (P < 0.001). No between-group differences were found (P > 0.05).

3.2.3. Brief pain Inventory (BPI)

The ANOVA showed a significant effect of time ($F_{(2,40)}$ = 5.456; *P* = 0.012) but not for group and time interaction (*P* = 0.245) for changes in BPI in pain score (Table 3). *Post hoc* analysis revealed significant within-group differences only in ac-tDCS group between pre- and post-intervention (*P* = 0.015). For the BPI function interference subscale, the ANOVA showed a significant effect for time ($F_{(2,40)}$ = 3.551; *P* = 0.045) but not for group and time interaction (*P* = 0.191). *Post-hoc* analysis did not show any significant within-group changes (P > 0.05; Table 3).

3.2.4. Widespread mechanical hyperalgesia (WMH)

The ANOVA revealed no significant time-related effects ($F_{(2,40)}$ = 1.188; *P* = 0.315) but instead a statistically significant interaction between group and time was found ($F_{(2,40)}$ = 7.190; *P* = 0.006) for changes in WMH (Fig. 2e; Table 3). *Post-hoc* analysis revealed significant differences between groups in favor of ac-tDCS group at follow-up (*P* = 0.017) with a large effect size (d = 1.11).

3.2.5. PPT locally and remote

The ANOVA did not show a significant effect for time ($F_{(2,40)}$ = 0.641; *P* = 0.53) neither for interaction between group and time ($F_{(2,40)}$ = 3.147;*P* = 0.06) for changes in local pressure pain threshold (Table 3). For PPT remote, the ANOVA did not show a significant effect for time ($F_{(2,40)}$ = 0.965; *P* = 0.365) but instead a statistically significant interaction between group and time was found

Table 2
Demographic and baseline characteristics

Characteristics	Active tDCS (N = 11)	Sham tDCS (N = 11)	P-value
Age, years, mean (SD)	66.27 (12.04)	60.18 (12.45)	0.25
Time with disease, years, mean (SD)	6.73 (5.75)	6.73(5.23)	1.00
Sex, n (%)			0.08
Female	4 (36.4%)	8 (72.7%)	
Male	7 (63.3%)	3 (27.3%)	
Side beginning, (right/left)	6/4	8/3	0.49
Hoehn & Yahr stage, N (%)			0.57
1	3 (27.3)	2 (18.2)	
2	2 (18.2)	7 (63.6)	
2.5	2 (18.29	0	
3	4 (36.4)	2 (18.2)	
UPDRS-III, score, mean (SD)	24.55 (11.69)	25.82 (10.33)	0.79
Levodopa equivalent daily dose, (mg)	1035.45 (413.91)	636.36 (324.31)	**0.02***
MMSE, mean (SD)	28.82 (1.25)	29.00 (1.09)	0.72
KPPS-D1, mean (SD)	9.36 (2.83)	9.27(2.53)	0.93
KPPS-D2, mean (SD)	3.64 (3.80)	7.91(8.28)	0.13
KPPS-D3, mean (SD)	9.73 (5.69)	8.45 (6.36)	0.62
KPPS-D4, mean (SD)	9.36(7.90)	6.00 (6.05)	0.27
KPPS-D5, mean (SD)	.82 (2.13)	2.00(3.34)	0.33
KPPS-D6, mean (SD)	8.36 (5.29)	5.82 (5.47)	0.28
KPPS-D7, mean (SD)	4.18 (5.54)	4.55 (4.29)	0.86
KPPS Total, mean (SD)	45.45 (20.80)	43.09 (22.43)	0.80
BPI pain, mean (SD)	20.82 (3.48)	19.64 (7.91)	0.65
BPI function interference, mean (SD)	37.91 (12.14)	38.55 (20.67)	0.93
BDI, mean (SD)	16.00 (7.92)	21.55 (12.87)	0.23
STAI-E, mean (SD)	29.27 (12.87)	37.18 (10.85)	0.12
STAI-R, mean (SD)	26.18 (10.54)	35.36 (14.39)	0.10
PCS, mean (SD)	25.18 (8.30)	29.73 (11.22)	0.30
TSK, mean (SD)	25.27 (5.60)	24.82 (6.32)	0.86
PPT locally, mean (SD)	2.06 (1.11)	2.42 (1.02)	0.42
PPT remote, mean (SD)	3.55 (0.76)	3.88 (1.29)	0.47
WMH, mean (SD)	5.61(1.54)	6.31 (1.88)	0.35
CPM PPT, mean (SD)	0.07 (.83)	0.33 (1.88)	0.54
TS, mean (SD)	20.36 (15.02)	25.55 (19.50)	0.50

Abbreviations: BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; CPM: Conditioned Pain Modulation; KPPS: Kińgs Parkinsońs Disease Pain Scale; MMSE: Mini-Mental State Examination; PCS: Pain catastrophizing scale; PPT: Pressure Pain Threshold; TS: Temporal Summation; TSK: Tampa Scale Kinesiophobia; UPDRS-III: Unified Parkinson's disease Rating Scale-III; WMH: Widespread Mechanical Hyperalgesia. * **P < 0.05**.

($F_{(2,40)}$ = 9.049; *P* = 0.002)(Fig. 2f; Table 3). *Post-hoc* analysis revealed significant differences between groups in favor of ac-tDCS group at post-intervention (*P* = 0.038) and at follow-up (*P* = 0.028) both with large effect size (d = 0.95 and d = 1.01, respectively).

3.2.6. Temporal Summation (TS)

The ANOVA did not show a significant effect for time nor for interaction between group and time were for changes in TS (*P* > 0.05).

3.2.7. Conditioned pain modulation (CPM)

The ANOVA revealed a significant effect for time ($F_{(2,40)}$ = 5.865; *P* = 0.012) and an interaction between group and time ($F_{(2,40)}$ = 4.113; *P* = 0.036) for changes in CPM (Fig. 2g; Table 3). *Post-hoc* analysis showed significant within-group differences only for ac-tDCS group between pre- and post-intervention (*P* = 0.002) and pre- and follow-up (*P* = 0.01). *Post-hoc* analysis showed significant differences between groups in favor of ac-tDCS group at post-intervention (*P* = 0.002) with a large effect size (d = 1.53) as well as at follow-up (*P* = 0.017; d = 1.11).

3.2.8. Sensitivity analysis

The ANCOVA results indicated that the factor LEDD did not interact with any of the effects found in any of the outcome measures (all P < 0.05).

3.2.9. Adverse effects

Adverse effects were mild and are shown in Supplementary Table 1. No significant between-group differences were found according to chi-squared tests (*P* > 0.05) for the presence of any adverse effects. No serious adverse effects or effects requiring health care intervention or hospitalisation were reported.

3.2.10. Appropriate blinding

The chi-square test revealed no between-group differences (X^2 (1) = 0.196, p = 0.658), suggesting blinding adequacy. In the placebo group (s-tDCS), 6 of 11 participants (54%) correctly guessed the group they belonged to (50%), while in the active group (ac-tDCS), 8 of 11 participants (72%). Therefore, our results support the use of the current blinding protocol (Dinn et al., 2017).

4. Discussion

This is the first triple-blinded randomized controlled trial applying tDCS to treat pain in PD patients. We showed that tDCS over M1 significantly reduced clinical perceived PD-related pain, improved the WMH, and enhanced the CPM compared with sham stimulation. However, tDCS over M1 did not significantly improve overall pain intensity or interference of pain, as assessed by the BPI, nor did it significantly reduce the TS after repetitive painful stimuli.

There are no studies assessing the effectiveness of tDCS on pain relief in PD patients, although it has been considered a potential rehabilitative intervention (Gandolfi et al., 2017). Despite the scarcity of scientific literature on the matter, previous neuroscientific evidence has provided insights into the neurophysiological processes that might explain our results. Basal ganglia dopaminergic neurodegeneration in PD provokes abnormalities in pain processing (Geroin et al., 2020), leading to hypersensitivity to pain and impairments of the descending inhibitory pathways (Thompson et al., 2017). Due to the strong connections between basal ganglia and cortical nociceptive areas, this neurodegeneration can be extended to non-dopaminergic structures such as posterior insula, thalamus and somatosensory cortex, affecting the sensitive-discriminative dimension of pain, and to the cingulate and the prefrontal cortices, impacting the affective-motivational sphere (Brefel-Courbon et al., 2005; Dellapina et al., 2012). On the one hand, it has been shown that anodic tDCS over M1 increases functional coupling between M1 and thalamus (Polanía et al., 2012), modulating the excitability in these areas obtaining effective pain relief (Knotkova et al., 2013). On the other hand, analgesic effects of tDCS have also been associated with attentional and emotional modulation of pain perception through the Dorsolateral Prefrontal Cortex and medulla, and subgenual Anterior Cingulate Cortex and insula, respectively (Yoon et al., 2014). Additionally, M1 stimulation simultaneously inhibits somatosensory cortex activity (Chiou et al., 2012) and finally it also promotes endogenous opioid release in areas of the pain neuromatrix (DosSantos et al., 2012). Hence, these neurophysiological correlations could explain why in our study tDCS applied over M1 was effective in patients with PD-related pain.

4.1. KPPS

Interestingly, improvements in KPPS were found significant only after 15 days of treatment, with a mean difference of 25.09

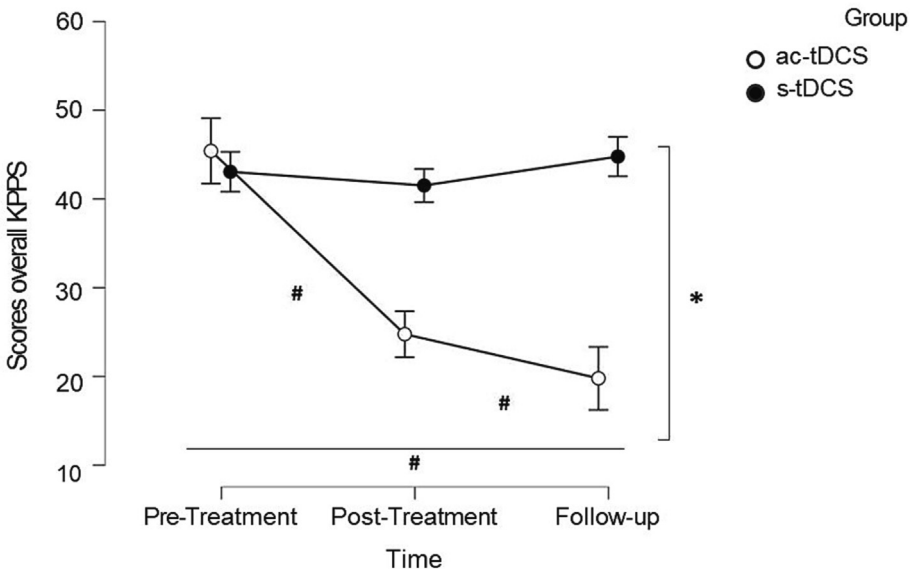

Fig. 2a. Clinical measures of included participants at different time points for KPPS overall score. Legend. Average Δ compared to Pre-treatment of KPPS overall score at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). KPPS: Kings Parkinsons Pain Scale; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. #= significant within group differences; *= significant between groups differences.

points, which is superior to its minimal clinically important difference ranging from 2.55–9.04 points (Taghizadeh et al., 2022).

Multiple studies have shown improvements of the KPPS after invasive or pharmacological therapies. Di Marzio et al. (DiMarzio et al., 2018) demonstrated that both subthalamic nucleus and Globus pallidus internus Deep Brain Stimulation could reduce the KPPS overall score at 6 months. Moreover, in line with our results, they also found a significant reduction in fluctuations-related pain and a trend towards improvement in nocturnal pain (DiMarzio et al., 2018). Subthalamic nucleus Deep Brain Stimulation most likely involves the descending inhibitory pain pathway through connections between the cingulate cortex and periaqueductal gray (Khazen et al., 2020). Interestingly, tDCS over M1 also modulates activity in the periaqueductal gray through connections with layer 5 M1 neurons (Dasilva et al., 2012; Gan et al., 2022), therefore, influence over descending pain pathways could be considered one potential mechanism through which tDCS alleviates pain in PD. Curiously, despite tDCS has been shown to improve neuropathic pain (Lefaucheur et al., 2017), no effects were found for "chronic pain" and "radicular pain" domains. A plausible explanation could be that in "visceral pain" item from "chronic pain" domain the scores of all patients, especially in the active group, were very low or even zero (meaning absence of this type of pain), which resulted in a floor effect in the domain. In the case of "radicular pain" domain, something similar occurred since there being only one item made a floor effect more likely. Nevertheless, both domains showed improvements in pain scores along the 3 measurements in the active group, but not enough to be statistically significant. Furthermore, in the original validation (Chaudhuri et al., 2015), four factors were extracted from the scale, and the domains of chronic pain and radicular pain were included within factors with more types of pain, suggesting that perhaps the classification by domains should be less segmented.

4.2. BPI

Despite the ac-tDCS group showing immediate improvements in their BPI pain intensity subscale scores compared to pre-intervention, the absence of significant differences with the s-tDCS group means we cannot definitively attribute these changes over time to the tDCS effect rather than a placebo effect that comes from simply being treated. The fact that KPPS overall improvements was not accompanied with reductions in BPI pain intensity subscale scores could be explained by methodological and content differences between these instruments. The KPPS evaluates seven different pain domains, so reductions in several of them could ultimately result in an overall improvement of the scale. In contrast, the BPI only asks about maximum, minimum, and average pain over the last 24 hours and the pain at that same moment. Therefore, we can hypothesize that improvements in the KPPS would be produced by specific significant improvements in fluctuations-related, nocturnal, and discoloration/swelling/edema associated pain, but may not result in an improvement in the maximum intensity of pain. Additionally, the KPPS evaluated the average of each type of pain over a recent period of time, providing a more complete evaluation of the patients' pain experience, whereas the BPI only asked about the pain in the last 24 hours. It could also be theorized that the improvements in the KPPS were the result of a reduction not only in intensity but also in the frequency of the different types of pain, which is not evaluated by the BPI.

4.3. WMH

Regarding WMH, its improvements were also significant 15 days post-intervention, however, we should interpret these results with caution because between-group differences could be reached after contrary trends in the time-effect in both groups. Additionally, upon analysing WMH in separate PPTs, a significant difference was only observed in the remote PPT, indicating a stronger effect on central rather than peripheral hyperalgesia.

There is a significant amount of heterogeneous literature on nociceptive thresholds in PD patients (Brefel-Courbon et al., 2005; Djaldetti et al., 2004; Ferreira-Sánchez et al., 2020; Gerdelat-Mas et al., 2007; Vela et al., 2012; Zambito Marsala et al., 2011). Nevertheless, most studies are not standardized in terms of assessment methodology or painful stimulus, making it difficult to draw robust conclusions. Our results were consistent with Marques et al. (Marques et al., 2013) who found improved

Table 3
Differences between active and sham treatments in primary and secondary outcome measures.

Variable	Baseline	Post-intervention	Between-group Difference Post-intervention		Follow-up	Between-group Difference Follow-up	
	Mean (SD)	**Mean SD**	**Mean difference (95% CI)**		**Mean (SD)**	**Mean difference (95% CI)**	
KPPS Total, score							
active-tDCS	45.46 (20.81)	24.73 (13.56)	−16.82	(−45.93, 12.35)	19.73 (11.58)	−25.09	(−54.20, 4.02)
sham-tDCS	43.09 (22.43)	41.55 (24.37)			44.82 (28.81)		
KPPS D1, score							
active-tDCS	9.36 (2.84)	6.27 (3.52)	−1.18	(−5.14, 2.78)	7.18 (3.55)	−1.36	(−5.33, 2.60)
sham-tDCS	9.27 (2.53)	7.46 (2.21)			8.56 (3.11)		
KPPS D2, score							
active-tDCS	3.64 (3.80)	1.82 (3.16)	−5.00	(−13.55, 3.55)	1.09 (2.43)	−6.09	(−14.64, 2.45)
sham-tDCS	7.91 (8.29)	6.82 (7.17)			7.18 (9.01)		
KPPS D3, score							
active-tDCS	9.73 (5.69)	5.82 (4.75)	−3.36	(−11.90, 4.46)	3.00 (4.12)	−7.27	(−15.10, 0.55)
sham-tDCS	8.455 (6.36)	9.18 (7.28)			10.27 (6.21)		
KPPS D4, score							
active-tDCS	9.36 (7.90)	4.55 (6.14)	−1.18	(−9.70, 7.34)	2.91 (4.35)	−3.36	(−11.88, 5.16)
sham-tDCS	6.00 (6.05)	5.73 (5.55)			6.27 (6.84)		
KPPS D5, score							
active-tDCS	0.82 (2.14)	1.00 (2.32)	−1.18	(−5.28, 2.92)	0.00 (0.00)	−2.36	(−6.46, 1.74)
sham-tDCS	2.00 (3.35)	2.18 (2.99)			2.36 (4.88)		
KPPS D6, score							
active-tDCS	8.36 (5.30)	3.18 (5.00)	−3.73	(−11.36, 3.90)	4.64 (4.95)	−2.82	(−10.45, 4.81)
sham-tDCS	5.82 (5.47)	6.91 (5.63)			7.46 (6.65)		
KPPS D7, score							
active-tDCS	4.18 (5.55)	2.09 (3.24)	−1.18	(−6.36, 4.00)	0.91 (1.64)	−1.82	(−7.00, 3.36)
sham-tDCS	4.55 (4.30)	3.27 (3.26)			2.73 (4.22)		
BPI (pain intensity), score							
active-tDCS	5.21 (0.87)	4.02 (1.42)	−0.55	(−3.01, 1.92)	4.52 (1.49)	0.00	(−2.46, 2.46)
sham-tDCS	4.91 (1.98)	4.57 (2.32)			4.52 (2.21)		
BPI (function interference), score							
active-tDCS	5.42 (1.74)	6.53 (7.94)	1.17	(−4.17, 6.51)	4.13 (1.72)	−1.08	(−6.42, 4.26)
sham-tDCS	5.51 (2.95)	5.36 (3.23)			5.21 (3.15)		
PPT (local), kg							
active-tDCS	2.06 (1.11)	2.50 (1.00)	0.54	(−0.71, 1.78)	2.34 (0.75)	0.64	(−0.61, 1.88)
sham-tDCS	2.43 (1.03)	1.97 (0.98)			1.71 (0.71)		
PPT (remote), kg							
active-tDCS	3.55 (0.77)	4.26 (1.49)	1.33	(−0.49, 3.14)	4.16 (1.84)	1.53	(−0.28, 3.50)
sham-tDCS	3.89 (1.30)	2.93 (1.31)			2.62 (1.11)		
WMH, kg							
active-tDCS	5.61 (1.54)	6.76 (2.33)	1.65	(−1.03, 4.33)	6.49 (2.17)	2.17	(−0.51, 4.85)
sham-tDCS	6.31 (1.88)	5.11 (2.28)			4.33 (1.70)		
TS, VNPRS							
active-tDCS	20.36 (15.02)	10.18 (20.71)	−9.36	(−30.85, 12.12)	20.36 (17.42)	3.91	(−17.57, 25.39)
sham-tDCS	25.55 (19.51)	19.55 (12.12)			16.46 (11.78)		
CPM, kg							
active-tDCS	0.08 (0.84)	1.35 (0.53)	0.95	(−0.22, 2.12)	1.64 (1.21)	1.14	(−0.03, 2.31)
sham-tDCS	0.34 (1.11)	0.40 (0.70)			0.50 (0.80)		

Abbreviations: BPI: Brief Pain Inventory; CPM: Conditioned Pain Modulation; D: Domain; KPPS: Kingś Parkinsońs Disease Pain Scale; PPT: Pressure Pain Threshold; TS: Temporal Summation; tDCS: Transcranial Direct Current Stimulation; VNPRS: Visual Numeric Pain Rating Scale; WMH: Widespread Mechanical Hyperalgesia.

pain thresholds with subthalamic nucleus Deep Brain Stimulation, relating these effects to changes in the sensory-discriminative and motivational-affective circuits by subthalamic nucleus' connection to the descending inhibitory pain system. Similarly, there is evidence that tDCS over M1 had effects on sensitive and emotional related structures such as the periaqueductal gray (Dasilva et al., 2012) and mediodorsal thalamic pathway (Gan et al., 2022). However, few studies have evaluated pain thresholds after tDCS application in neurological patients.

4.4. CPM

We found that, tDCS over M1 could improve CPM immediately and after 15 days. In fact, previous studies correlate a more altered

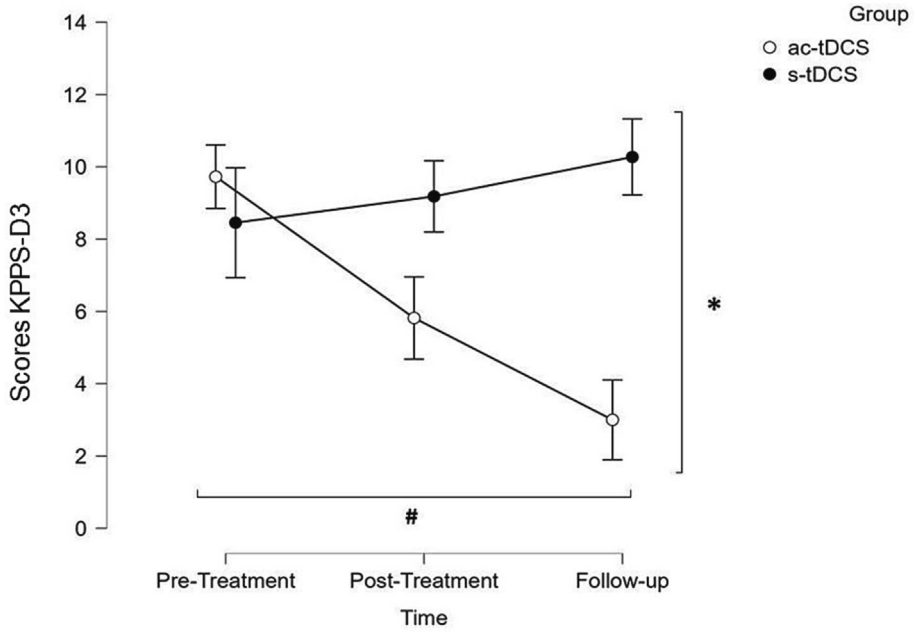

Fig. 2b. Clinical measures of included participants at different time points for KPPS-D3 score. Legend. Average Δ compared to Pre-treatment of KPPS-D3 score at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). KPPS-D3: Kińgs Parkinsońs Pain Scale Domain 3; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. #= significant within-group differences; *= significant between groups differences.

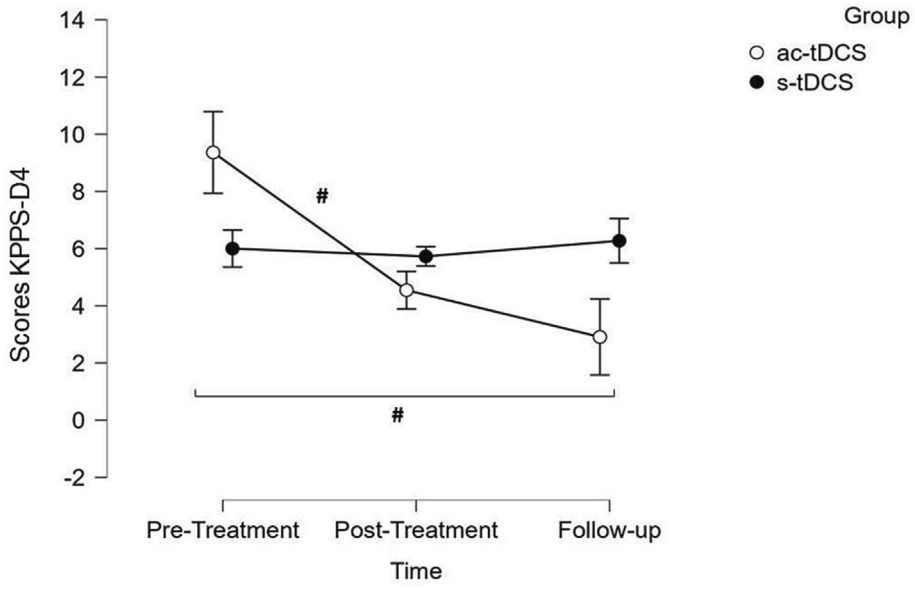

Fig. 2c. Clinical measures of included participants at different time points for KPPS-D4 score. Legend. Average Δ compared to Pre-treatment of KPPS-D4 score at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). KPPS-D4: Kińgs Parkinsońs Pain Scale Domain 4; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. #= significant within-group differences.

CPM with a greater increase in pain severity in patients with PD (Granovsky et al., 2013), which could explain why the immediate improvement in CPM in our study indirectly improved the severity of clinical pain perceived after 15 days. Moreover, there are differences in the protocols used to measure CPM across studies (Granovsky et al., 2013; Grashorn et al., 2015). We followed the most appropriate paradigm (pressure for test stimulus and cold for conditioning stimulus) according to the study by Imai et al. (Imai et al., 2016). The results obtained can be influenced by the CPM paradigm used (Grashorn et al., 2015); therefore, it is essential to standardize the measurement of this variable in future studies involving patients with PD. Our study, as opposed to those comparing CPM between PD patients and healthy controls, specifically evaluated CPM in PD patients experiencing pain. This ties in well with the identification of a noradrenergic PD phenotype that leads to early dysfunction of noradrenergic transmission in both the central and peripheral nervous system circuits that results in a specific cluster of non-motor symptoms, including pain (Ray

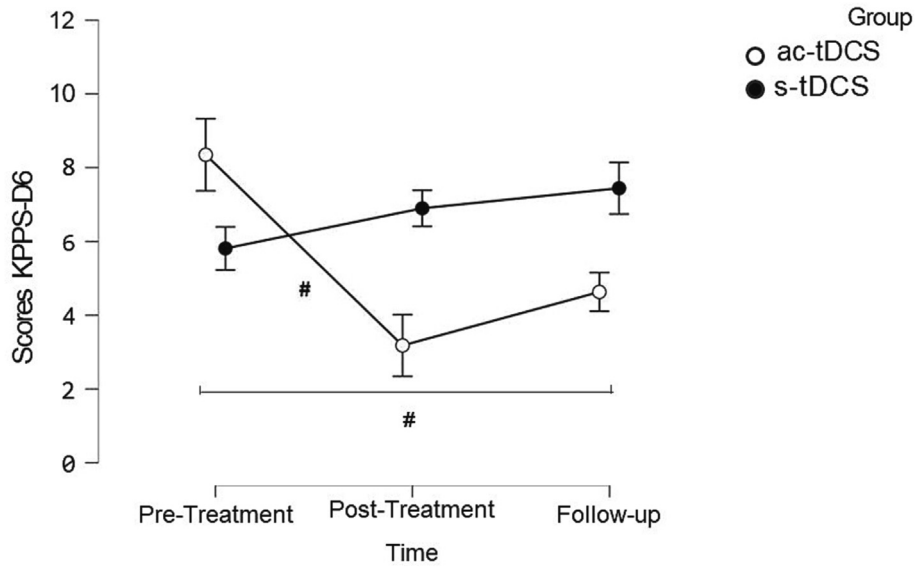

Fig. 2d. Clinical measures of included participants at different time points for KPPS-D6 score. Legend. Average Δ compared to Pre-treatment of KPPS-D6 score at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). KPPS-D6: Kińgs Parkinsońs Pain Scale Domain 6; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. #= significant within-group differences.

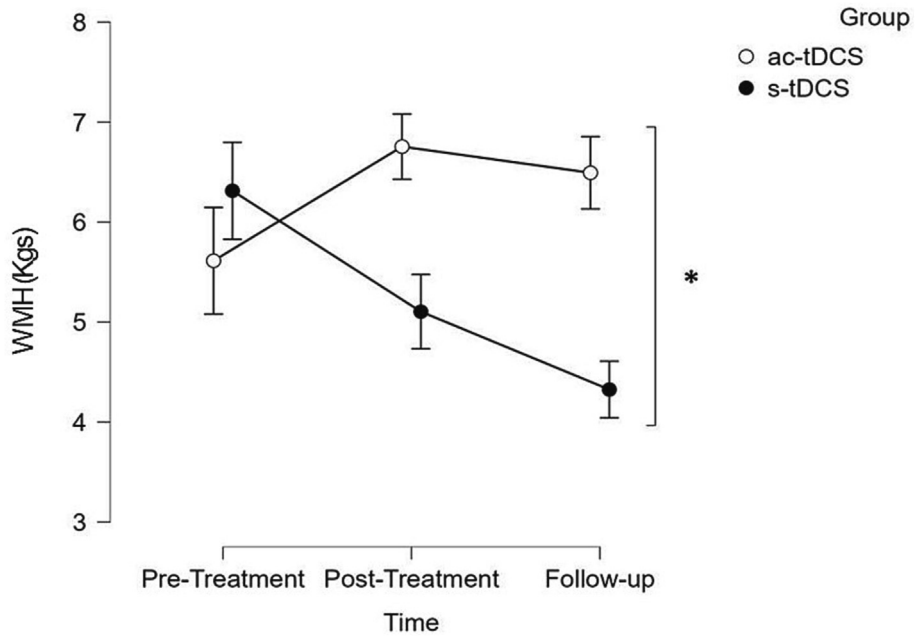

Fig. 2e. Clinical measures of included participants at different time points for WMH. Legend. Average Δ compared to Pre-treatment of WMH at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). WMH: widespread mechanical hyperalgesia; Kgs: kilograms; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. *= significant between groups differences.

Chaudhuri et al., 2023). Therefore, the improvement seen in our study can be explained by the fact that tDCS might be capable of modulating the activity of neurodegenerated noradrenergic structures involved in descending pain inhibition, such as the periaqueductal gray and locus coeruleus (Dasilva et al., 2012; Kucharczyk et al., 2022), thus normalizing these systems and providing effective pain relief.

4.5. TS

Finally, tDCS over M1 was ineffective for ameliorating TS of pain neither immediately nor at 15 days follow-up in PD patients. It has been shown these patients have increased TS when compared to healthy subjects, indicating diffuse facilitation of painful stimuli that may be associated with the presence of Lewy bodies in the dorsal horn of the spinal cord (Boura et al., 2017; Perrotta et al., 2011). However, this increase in TS has not been correlated with the presence of pain, and the effects of dopamine have been contradictory (Avenali et al., 2017; Perrotta et al., 2011). One possible explanation for the clinical improvement in pain perception and activation of descending pain inhibitory systems, but not in nociceptive TS, would be that tDCS over M1 may activate cortical and supraspinal areas directly associated with descending pain inhibition (Cury et al., 2020), but without influencing on the nociceptive

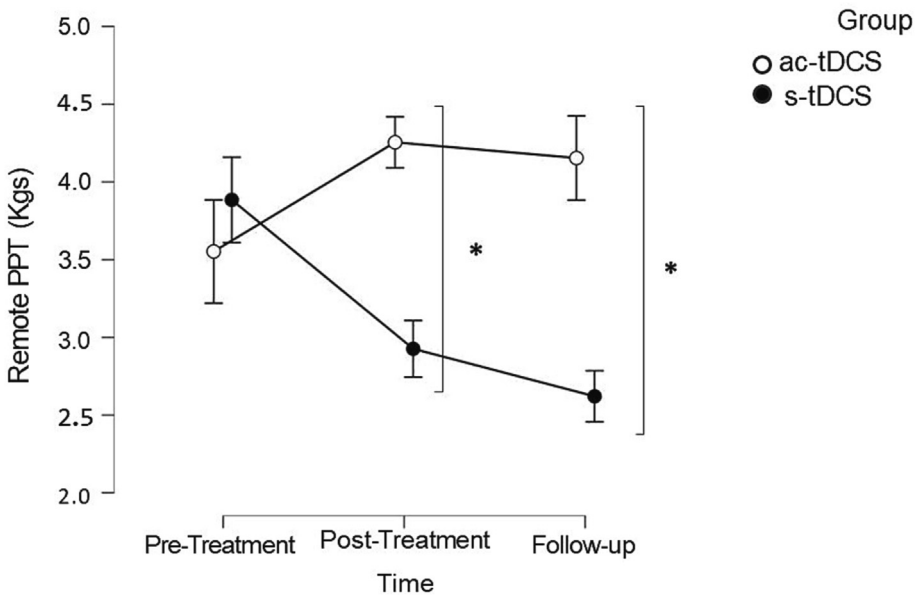

Fig. 2f. Clinical measures of included participants at different time points for remote PPT. Legend. Average Δ compared to Pre-treatment of remote PPT at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). PPT: pain pressure threshold; Kgs: kilograms; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. *= significant between groups differences.

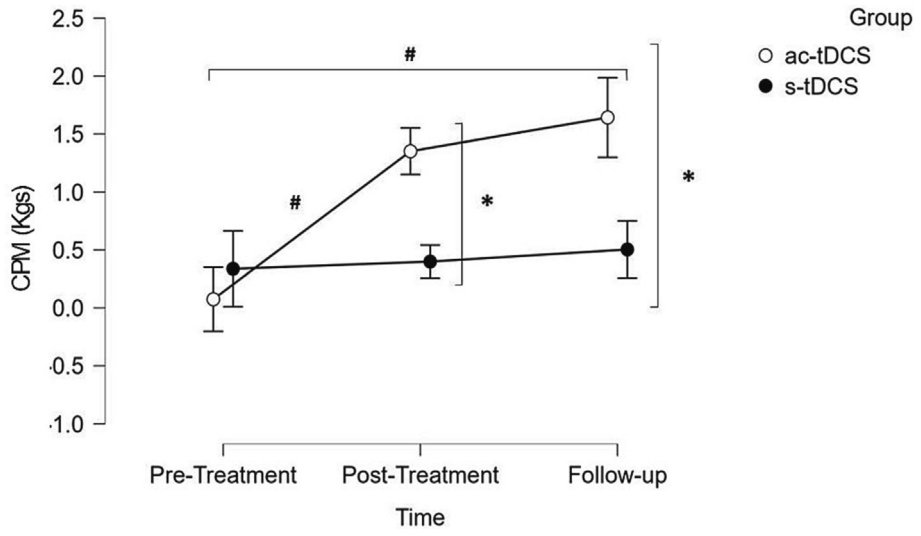

Fig. 2g. Clinical measures of included participants at different time points for CPM. Legend. Average Δ compared to Pre-treatment of CPM at Post-treatment (2 days after 10 consecutive daily sessions of either ac-tDCS or s-tDCS from Monday to Friday), and at Follow-up (15 days follow-up). CPM: conditioned pain modulation; Kgs: kilograms; ac-tDCS: active transcranial direct current stimulation; s-tDCS: sham transcranial direct current stimulation. #= significant within group differences; *= significant between groups differences.

output generated in the dorsal horn of the spinal cord. In normal conditions, such activation of descending inhibition could improve excitability by itself, but in patients with PD, it may be necessary to generate greater influence on the hyperexcitability present in central nociceptive pathways. Some studies have assessed TS after tDCS application in healthy subjects with contradictory results (Braulio et al., 2018; Gurdiel-Álvarez et al., 2021; Hughes et al., 2019; Kold and Graven-Nielsen, 2023).

Among limitations are the significant statistical differences between the two treatment groups at the baseline LEDD, which could potentially affect the results of the tDCS treatment. Although there are no studies that demonstrate that levodopa could influence this effect, and each patient has their own proper dose adjustment, it would be important to consider these differences in future studies. Secondly, the lack of categorization of patients into nociceptive, neuropathic, or nociplastic pain types, as well as not differentiating these three types in the data analysis, limits insights into which would have benefited more from tDCS treatment. However, the goal was more directed towards classifying and analysing the specific types of PD-related pain according to the KPPS. Thirdly, the follow-up period was relatively short, only 15 days, which is not sufficient to capture any potential long-term effects. Finally, all evaluations and treatments were conducted with patients in the ON state, which may neglect the effects in the OFF state. However, assessments during ON state were performed to isolate tDCS effects from levodopa's due to our goal was to optimize the treat-

ment for symptoms unresponsive to individualized levodopa dosages. Identifying tDCS's symptom management boost beyond standard medication is crucial. This optimizes outcomes for less-responsive symptoms to patient-specific levodopa dosing.

5. Conclusion

We found that tDCS over M1 effectively reduced clinical perceived pain, improved WMH, and enhanced CPM compared to sham stimulation. However, tDCS did not significantly improve overall pain intensity, pain interference nor TS. Interestingly, improvements in PD-pain and WMH were observed after 15 days of treatment, while CPM enhancement was immediate and sustained. Further studies with larger sample sizes, longer follow-up periods, and additional evaluation in the OFF state are needed.

CRediT authorship contribution statement

Yeray González-Zamorano: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Francisco José Sánchez-Cuesta:** Data curation, Validation. **Marcos Moreno-Verdú:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Aida Arroyo-Ferrer:** Data curation, Validation. **Josué Fernández-Carnero:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **K. Ray Chaudhuri:** Validation, Writing – review & editing. **Anna Fieldwalker:** Validation, Writing – review & editing. **Juan Pablo Romero:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing.

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None of the rest of authors has financial disclosures to declare.

Declaration of competing interests

The authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.01.011.

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