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Transcranial Direct Current Stimulation in Parkinson's Disease Patients in the Off State: A Randomized Controlled Crossover Trial Examining the Effects on Pain With and Without the Influence of Dopaminergic Medication

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Keywords: dopaminergic medication | off state | pain | Parkinsons disease | transcranial direct current stimulation

ABSTRACT

Background: tDCS has demonstrated hypoalgesic effects on Parkinson's disease (PD)-related pain applied in the On state but not in the Off state. We aimed to determine the effect of tDCS in the Off state followed by dopaminergic medication on PD-related pain.

Methods: This randomized controlled crossover trial included 15 patients (age range 39–81, 5 male) with PD-related pain in the Off state. All participants received both an active and sham tDCS sessions of 20 min over the M1 contralateral to pain at 2 mA intensity in two separate days while in Off state. Following tDCS they took its dopaminergic medication. Outcome measures were assessed at baseline, post-tDCS and post-medication intake. The Numeric Pain Rating Scale (NPRS), Global Rating Of Change (GROC), Conditioned Pain Modulation (CPM), Pain Pressure Thresholds (PPT) and Widespread Mechanical Hyperalgesia (WMH) were evaluated.

Results: No significant differences were found after active tDCS in NPRS, GROC, CPM, PPT's or WMH when compared to sham at post-medication intake measure. However, examining exclusive effects of tDCS in the Off state for NPRS, active tDCS was superior to sham tDCS ($p = 0.037$). No meaningful changes between stimulation conditions were found in GROC, CPM, PPT's and WMH at post-tDCS measure.

Conclusions: One session of tDCS over the M1 alleviates pain perception in PD patients in the Off state. However, tDCS followed by dopaminergic medication intake does not yield additional benefits in pain processing suggesting pathways different to dopaminergic ones in pain regulation in PD patients. These findings are exploratory and carry high risk of type-II error.
Trial Registration: clinicaltrials.gov identifier: NCT06214377

1 | Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by several motor and non-motor symptoms [1]. Notably, individuals with PD often experience two contrasting states. The "On" state occurs when dopaminergic medication is effectively working, leading to improved symptoms. Conversely, the "Off" state happens when these medications are not providing effects, resulting in a resurgence of more severe symptoms. Fluctuations in both states are frequent and affect non-motor symptoms.

Pain is one of the most prevalent and disabling non-motor symptoms [2], present in 40% to 85% of cases [3, 4]. Dopaminergic dysregulation has a potential key role in the potentiation of nociceptive signals and its interpretation as pain thresholds have been observed to fluctuate with dopamine in previous studies [5].

PD patients in the Off state exhibit pain hypersensitivity compared to healthy individuals [6, 7]. Interestingly, dopaminergic medication may not inherently alleviate pain but normalizes the heightened pain sensitivity seen in the Off state. Additionally, PD patients experience enhanced central nociceptive facilitation [8] and deficits in descending inhibitory pathways, likely tied to neurodegeneration in cortical and brainstem areas that control pain modulation [9]. While dopaminergic medication alone has shown controversial findings regarding improving central hypersensitivity (Avenali et al., 2017) [10] and pain modulation [11], treatments like transcranial direct current stimulation (tDCS) have demonstrated promising results [12].

TDCS is a non-invasive brain stimulation technique [13]. The application of tDCS over the primary motor cortex (M1) is theorized to alleviate pain by enhancing excitability across various structures involved in pain processing, through cortico-subcortical connectivity [14]. TDCS has been shown to relieve pain and improve psychophysical pain measures in chronic pain populations [15, 16]. Previous work has demonstrated that 10 sessions of tDCS over M1 alleviated pain perception, pain sensitivity, and enhanced descending inhibitory pathways in PD patients in the On state [12].

Based on the previous findings, we hypothesize that the application of tDCS in the Off state of PD patients, prior to dopamine, could exert a neuromodulatory effect on dopaminergic transmission [17], thereby enhancing the effect of dopaminergic medication in pain improvement. This hypothesis aligns with findings related to the enhancement of motivational-affective endogenous pain modulation through the reward circuits activated by dopaminergic medication, since tDCS could act as a neuromodulatory technique and amplify these effects [11].

There is currently no evidence evaluating the effect of tDCS over dopaminergic medication in PD patients in the Off state for pain control, making it pertinent to conduct this trial. We aimed to determine the effect of a single session of tDCS over M1 followed by usual dopaminergic medication on perceived pain and pain processing characteristics in PD patients. Our secondary objective was to determine those effects following tDCS application in the Off state of patients.

2 | Methods

2.1 | Study Design and Participants

This was a triple-blinded, placebo-controlled, randomized crossover trial, reported as per recommendations of The Consolidated Standards of Reporting Trials (CONSORT) [18, 19]. The trial was registered prospectively at clinicaltrials.gov (ID: NCT06214377). Ethical approval was obtained from Hospital Universitario 12 de Octubre (Madrid, Spain, N° CEIm: 23/032) and the study was conducted according to the Declaration of Helsinki [20].

Individuals with idiopathic PD, based on the United Kingdom PD Society Brain Bank criteria, suffering from PD-related otherwise unexplained pain checked by step one of the Parkinson's Disease Pain Classification System [21], and presenting fluctuations-related pain confirmed by domain 3 of the King's Parkinson's Pain Scale (KPPS) [22] were enrolled. The remaining eligibility criteria are listed in Table 1. Written informed consent was obtained and signed from all participants prior to enrollment.

The sample size calculation of the present study was performed using the G*Power software. The effect size obtained after 10 sessions of the same tDCS protocol in patients with PD-associated pain in the On state for the variable Conditioned Pain Modulation (CPM) ($d = 1.089$) in a previous study was taken as a reference [12]. However, assuming that the effect size for a single treatment session instead of 10 sessions would be smaller, we considered a $d = 0.8$. It was calculated for a mean difference test using a paired *T*-test (due to the crossover design), with two tails based on an effect size $d = 0.8$, with a statistical power of $1-\beta = 0.8$ and $\alpha = 0.05$. The final sample size calculation indicated that 15 subjects were necessary.

2.2 | Procedures

Each participant attended two tDCS sessions, one with the experimental condition (active tDCS) and another with a simulated condition (sham tDCS), serving as their own control. During each intervention, participants were seated comfortably [23] and monitored for any potential adverse effects using the Comfort Rating Questionnaire [24, 25]. Both treatment sessions were separated by a washout period of 7–12 days, which exceeds the duration of the after-effects of a single

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Older than 18	Neuroimaging study presenting previous pathologies
Functional capacity to undergo the protocol (Barthel Score > 5 in transfers bed to chair and back)	Dermatologic issues, wounds, or ulcers in the scalp
Score ≥ 25 in Montreal Cognitive Assessment (MoCA)	Presence of metal implants or brain stimulators in the head
Tolerability for the application of electrotherapy	Presence of cardiac pacemaker, medication pumps, ventriculoperitoneal shunts or aneurysm clips
Able to provide informed consent to participate in the study	Limited language expression
	History of alcohol or drugs abuse
	Uncontrolled medical problems
	Pregnancy
	Epilepsy

tDCS session [13], to avoid potential carryover effects. All safety and replicability guidelines were strictly followed [26]. Within each session, patients were evaluated in the Off state (pre-tDCS), so that they were instructed to refrain from taking any dopaminergic medications the night before testing, followed by the tDCS condition treatment and a second evaluation (post-tDCS). Afterwards, patients took their usual first morning dopaminergic dose and waited until they reached the On state (30–60 min after administration and after explicit confirmation of symptom improvement) and were finally re-evaluated (post-medication). The schematic representation of the procedure is shown in Figure 1.

2.3 | Randomization and Masking

The assignment to treatment order (active-sham vs. sham-active tDCS) was randomized by an independent researcher using the GraphPad software (GraphPad Software, San Diego, CA, USA). Triple-blind criteria were achieved by identical collocation of the electrodes in both treatments and by activating the "double-blind" option in the software NIC2 (Neuroelectrics Inc., Barcelona, España) that allows hiding the protocol with a neutral code. An independent researcher concealed the allocation following the neutral code assignment using sealed and opaque envelopes that were opened each day at the time of the intervention. The therapist and the evaluator ignored the code assignment, preventing them from knowing the condition applied.

2.4 | Interventions

2.4.1 | Active tDCS

Stimulation was administered using the Starstim tDCS device equipped with saline-soaked sponge electrodes (35 cm^2). The placement of the anode electrode was on C3 or C4 (EEG 10/20 international system), while the cathode was positioned over the opposite supraorbital area (Fp2 or Fp1), targeting the M1 area contralateral to the pain site [13, 27]. In cases of bilateral or symmetric pain, stimulation was applied over the left M1, as this configuration has been shown to induce widespread modulation across both hemispheres, including contralateral M1 and associated pain-processing regions [28]. The stimulation involved a consistent 2 mA current for 20 min, which included a gradual increase and decrease over 30 s [29]. This tDCS targeting protocol is supported by recent evidence highlighting M1's role in pain modulation via enhanced functional connectivity with the thalamus, basal ganglia, periaqueductal grey, and other key nodes of the descending antinociceptive system such as the anterior cingulate cortex, dorsolateral prefrontal cortex, and insula [30–33].

2.4.2 | Sham tDCS

The electrodes for sham stimulation were arranged identically as those used for active stimulation. After the initial ramp-up phase of 30 s with active current, the stimulator was then switched off. This procedure allowed participants to feel the initial tingling sensation, but no actual current was delivered for the remainder of the session. This method of sham stimulation has been effectively used to blind subjects [34].

2.5 | Outcomes

The outcome measures adhered to the guidelines set by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) guidelines [35].

2.5.1 | Sociodemographic and Clinical Characteristics

At baseline, age, sex, years with PD, side of onset of symptoms, Levodopa Equivalent Daily Dose (LEDD), and Hoehn and Yahr Stage were collected [36, 37]. Unified Parkinson's Disease Rating Scale Part-III (UPDRS-III) was evaluated at two time points (pre-tDCS and post-medication). Regarding pain intensity, location, fluctuations, and interference, the Spanish-King's Parkinson's Pain Scale (KPPS) and the short-Brief Pain Inventory (BPI) were used [38–40], whereas motor complications were assessed with the UPDRS Part-IV (UPDRS-IV) [41, 42]. Furthermore, the Tampa Scale for Kinesiophobia (TSK-11) [43], Pain Catastrophizing Scale (PCS) [44], Beck Depression Inventory-II (BDI-II) [45], State–Trait Anxiety Inventory (STAI) [46], and Montreal Cognitive Assessment (MoCa) [47] were employed. The permission to use the MoCA scale in our research was granted.

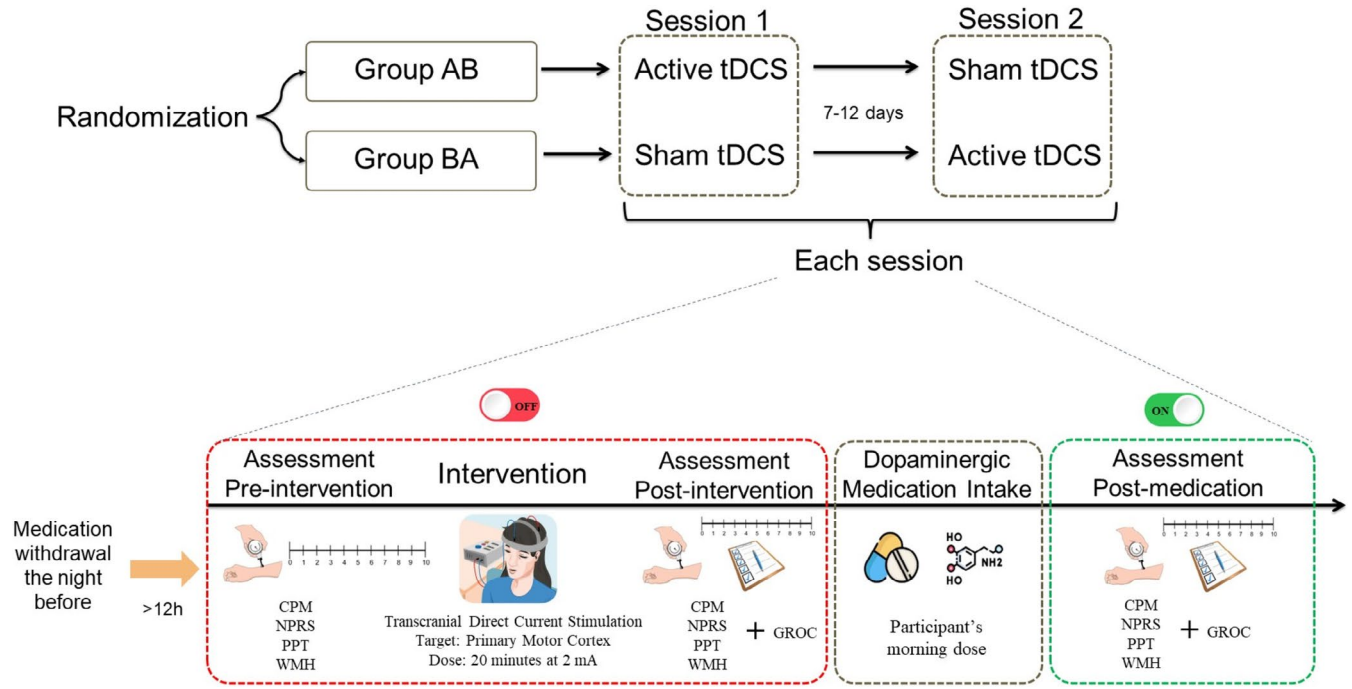

FIGURE 1 | Schematic representation of the experimental procedure. CPM, Conditioned Pain Modulation; GROC, Global Rating Of Change; NPRS, Numeric Pain Rating Scale; PPT, Pain Pressure Threshold; tDCS, transcranial Direct Current Stimulation; WMH, Widespread Mechanical Hyperalgesia.

2.5.2 | Psychophysical Variables

2.5.2.1 | Pressure Pain Threshold (PPT). The PPT was assessed using a hand-held pressure algometer with a 1-cm diameter flat rubber probe (Model FDIW, Wagner Instrument Mark). One point was marked in the patient's main pain area to evaluate local (peripheral) hyperalgesia, and another on the nail bed of the right thumb to evaluate remote (central) hyperalgesia, as this location has already been used in previous studies [48]. The algometer was placed perpendicular to the skin, and the force was increased at a rate of 1 kg/s. The patient was told to indicate when the sensation changed from pressure to pain. Three measurements were taken at each point, with a 30-s separation between them, and the mean of the three measurements was used for statistical analysis. The validity and reliability of this procedure have shown good clinometric properties [49, 50].

2.5.2.2 | Widespread Mechanical Hyperalgesia (WMH). The WMH was calculated by adding up the means of the two PPT locations [51]. Lower values were associated with a more pronounced WMH, while higher values indicated absence of WMH.

2.5.2.3 | Conditioned Pain Modulation (CPM). CPM was assessed with a 5-min interval from the PPT protocol to avoid potential contamination. PPT was assessed at the nail bed using the same algometer, serving as the first test stimulus. Subsequently, the patient immersed their opposite hand in a "cold pressor" (0°C–4°C) (conditioning stimulus) up to the wrist level and maintained that position for 3 min (if pain became intolerable, the patient could withdraw the hand earlier). Verbal confirmation from patients of moderate to severe pain induction was needed. Once the hand was withdrawn from the cold pressor, a second PPT measurement was taken at the same location as the first (second test stimulus) [52]. The combination of algometry and the "cold pressor task" has demonstrated to be the most reliable method for assessing CPM [53].

2.5.2.4 | Pain Intensity. Pain intensity was evaluated with the Numeric Pain Rating Scale (NPRS). NPRS is scored using numbers on a Likert scale ranging from 0 (no pain) to 10 (worst pain imaginable, inability to perform daily activities). This tool has shown good reliability [54].

2.5.2.5 | Global Rating of Change (GROC). The GROC was used to measure the extent to which a patient perceives that it has improved or worsened over a specific time. It involves a single question posed to the patient to rate their change in comparison to the pre-intervention state, ranging from −7 (much worse than before), through 0 (same as before), to +7 (much better than before). The GROC has been shown to a be valid and reliable [55, 56].

2.6 | Statistical Analyses

All analyses were performed in R version 4.3.2 [57]. The R packages used are described in Supporting Information. Descriptive statistics were performed by mean and SD for continuous variables and relative frequencies for categorical variables. For statistical analyses, 95% confidence intervals (95% CI) were obtained for parameter uncertainty, and alpha = 0.05 was set for statistical significance.

Paired samples *t*-tests were first used to compare baseline pain levels (NPRS) between sham and active tDCS sessions as well as a consistent effect of levodopa intake on motor symptoms (UPDRS-III), and therefore an Off-to-On change.

To test the hypothesis of an exclusive or additional effect of tDCS to levodopa (i.e., a difference between sham and active tDCS treatments), we first conducted a paired samples *t*-test for the main outcome measure (CPM) according to our sample size calculation procedure. Afterwards, a linear mixed-effects model (LMM) was used, including participants as random effects (i.e., as random intercepts), the average baseline across sessions (i.e., pre-tDCS measurement in sham and active sessions) as a covariate, and accounting for the effects of period (first or second) and period by treatment interaction (i.e., carry-over effect or sequence effect) by including them as covariates. Each LMM was built with the following structure: y~(1|Participant) + Treatment + Sequence + Period + Baseline, where y was the outcome measure at post-medication.

Regarding the GROC scale, LMMs were applied to the pre to post-tDCS change, pre to post-medication change, and post-tDCS to post-medication. These models did not include any baseline covariate as the GROC scale is a measure of change and therefore was not administered at baseline.

Standardized effect sizes between active and sham tDCS were computed as Hedges' g for paired observations and interpreted as small, medium, or large if $g < 0.3$, 0.3–0.8, and > 0.8, respectively.

Sensitivity analyses were performed to remove potential outliers in all the LMMs using Cook's distance. Observations were removed if Cook's $D > 0.5$.

3 | Results

None of the trial methods changed after the study's beginning. Eighteen potential participants were contacted to participate between May and December 2023. Fifteen participants were finally recruited and completed both intervention sessions (Figure 2) with a mean difference of 8.33 (1.88) days between them. No data were lost across sessions and assessments for any of the outcomes. Sociodemographic, clinical, and psychosocial characteristics are shown in Table 2.

3.1 | Pain Levels at Baseline

Baseline NPRS scores for sham and active sessions, regardless of sequence, were positively and moderately correlated ($r = 0.57$, $p = 0.028$), and were not different (mean difference (MD) = 0.93 points, 95% CI [−0.33, 2.20], $t(14) = 1.58$, $p = 0.137$). Considering the sequence, the groups did not differ in baseline NPRS scores for sham (MD = 0.97 points [−1.69, 3.63], $t(14) = 0.79$, $p = 0.444$) or active (MD = 0.58 points [−2.45, 3.62], $t(14) = 0.416$, $p = 0.684$) tDCS sessions. Therefore, the analyses based on a cross-over design were justified.

3.2 | Effect of Levodopa: Motor Changes From Off to on State

UPDRS-III scores at baseline and post-medication were strongly correlated both for the sham ($r = 0.89$, $p < 0.001$) and active ($r = 0.87$, $p < 0.001$) tDCS sessions. Thus, a paired samples *t*-test was justified. Overall, a clinically significant improvement was found after levodopa intake, as it produced a substantial reduction in UPDRS-III scores in On versus Off states, both in the sham (MD = −6.27 points [−3.96, −8.57], $t(14) = -5.82$, $p < 0.001$) and active (MD = −6.06 points [−3.27, −8.86], $t(14) = -4.67$, $p < 0.001$) tDCS sessions. Importantly, these differences were of equivalent magnitude between sham and active tDCS sessions (MD = 0.2 [−2.07, 2.47], $t(14) = 0.19$, $p = 0.853$), confirming a stable effect of levodopa. UPDRS-III scores are shown in Table S1. There were no differences between active and sham tDCS in the time between medication intake and the reported On state (MD = −1.87 min [−7.91, 4.18], $t(14) = -0.66$, $p = 0.519$).

3.3 | Additional Effect of tDCS on Levodopa on Pain Measures: Effects at on State

Group averages for Off and On states during active and sham tDCS sessions are shown in Table 3 and participant scores for pain measures in Table S2. Mean differences between active and sham tDCS sessions, by sequence, are shown in Table S3. Model summaries for all the LMM can be found in Table 4. The ANOVA table of main effects for each outcome measure, considering the models at On state, is shown in Table S4. Effect sizes in On state are shown in Table S5.

According to the paired samples *t*-test, there were no additional effects of tDCS on levodopa, as shown by a lack of statistically significant differences between active and sham tDCS for CPM (MD = −0.6 kg [−2.19, 0.99] (Figure 3A), $t(14) = -0.81$, $p = 0.432$). This was confirmed after adjusting for period, treatment by period interaction, baseline measures, and inter-individual variability in the LMM (MD = −0.8 kg [−2.06, 0.46], $F(1,25) = 1.71$, $p = 0.203$).

For NPRS, active tDCS was not superior to sham tDCS (MD = −0.64 points [−1.57, 0.29], $F(1,11.99) = 2.04$, $p = 0.178$) (Figure 3B). The same was found for local PPT (MD = 0.22 kg [−0.65, 1.09], $F(1, 25) = 0.27$, $p = 0.608$) (Figure 3C), the remote PPT (MD = 0.08 kg [−0.63–0.78], $F(1, 12.61) = 0.05$, $p = 0.826$) (Figure 3D), or the WMH (MD = 0.33 kg [−1.07–1.74], $F(1, 25) = 0.24$, $p = 0.628$) (Figure 3E). For the GROC scale, neither the change from baseline (pre-tDCS) to On state nor from post-tDCS to post-medication (On state) revealed a significant difference between active and sham tDCS (Table S6).

3.4 | Exclusive Effect of tDCS in Off State: Immediate Effects

Group averages for pain measures, for pre and post-tDCS during active and sham tDCS sessions in Off state, are shown in Table 5,

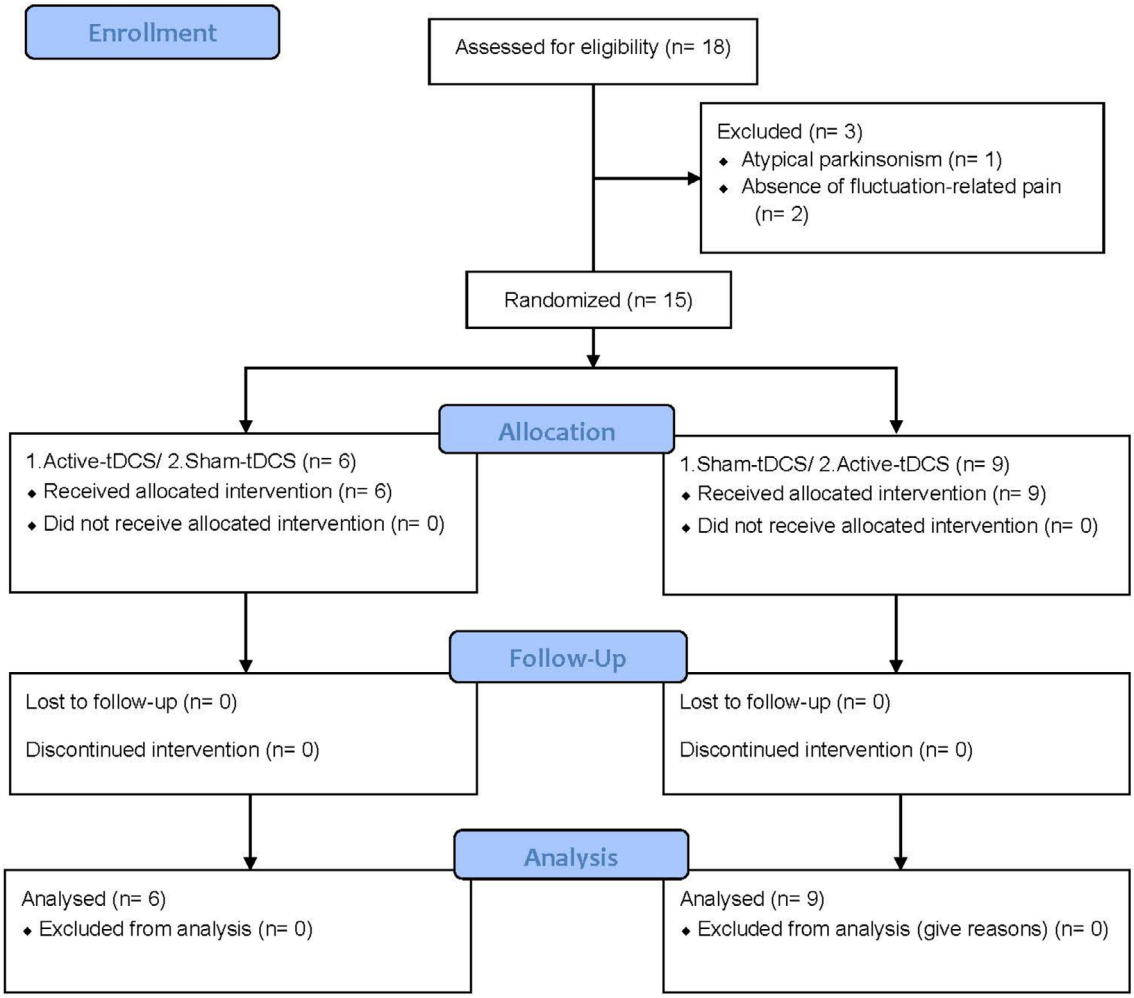

FIGURE 2 | Consort flow diagram of study participants.TDCS, transcranial Direct Current Stimulation.

and participant scores for pain measures in Table S7. Mean differences between active and sham tDCS sessions, by sequence, are shown in Table S8. Model summaries for all the LMM can be found in Table 6. The ANOVA table of main effects for each outcome measure, considering the models at post-tDCS, is shown in Table S9. Effect sizes at post-tDCS are shown in Table S10.

According to the paired samples *t*-test, there were no statistically significant differences between active and sham tDCS for CPM (MD = −0.87 kg [−2.44, 0.71], t(14) = −1.18, $p = 0.259$) (Figure 3A). This was confirmed after adjusting for period, treatment by period interaction, baseline measures, and inter-individual variability in the LMM, although a trend towards more improvement for sham was found (MD = 1.06 kg [−2.33, 0.21], F(1,25) = 2.98, $p = 0.097$).

For NPRS, active tDCS was superior to sham tDCS (MD = −1.28 points [−2.48, −0.08], F(1,25) = 4.876, $p = 0.037$) (Figure 3B). For the local PPT, no differences were found (MD = 0.14 kg, [−0.39, 0.67], F(1, 25) = 0.29, $p = 0.593$) (Figure 3C). For the remote PPT, a trend towards an increased threshold for active tDCS was found (MD = 0.37 kg [−0.06, 0.8], F(1, 25) = 3.13, $p = 0.090$) (Figure 3D). For WMH, no differences were found (MD = 1.01 [−0.27, 2.29], F(1, 25) = 2.64, $p = 0.117$) (Figure 3E). The same was found for the GROC (Table S6).

3.5 | Sensitivity Analyses

Based on Cook's distance (Table S11), for the LMMs analyzing the additional effect of tDCS on levodopa, all models were re-run after dropping $N = 1$–2 observations from 1 to 2 participants. The results are shown in Table S12 and were equivalent to the main analysis.

Cook's D for the LMMs analyzing the exclusive effect of tDCS (i.e., at post-intervention immediately after tDCS) is shown in Table S13. Only the models for CPM ($N = 2$ observations from 2 different participants), remote PPT ($N = 1$ observation), and WMH ($N = 1$ observation) were re-run. The results are shown in Table S14 and were equivalent to the main analysis.

Based on Cook's distance (Table S15), for the LMMs analyzing the GROC, only the model considering post-tDCS to post-medication changes was re-run ($N = 4$ observations). The results are shown in Table S16 and were equivalent to the main analysis.

TABLE 2 | Sociodemographic, clinical, and psychosocial characteristics of the participants.

Characteristic	Active-Sham ($N=6$)[a]	Sham-Active ($N=9$)[a]	Overall ($N=15$)[a]
Sex			
Female	3 (50%)	7 (78%)	10 (67%)
Male	3 (50%)	2 (22%)	5 (33%)
Age, years	61.00 ± 14.74	61.00 ± 9.04	61.00 ± 11.15
Time with disease, years	5.00 ± 2.37	8.11 ± 4.08	6.87 ± 3.74
Hoehn & Yahr stage			
2.0	1 (17%)	4 (44%)	5 (33%)
2.5	1 (17%)	2 (22%)	3 (20%)
3.0	4 (67%)	3 (33%)	7 (47%)
LEDD, mg	818.25 ± 360.95	1058.64 ± 527.70	962.48 ± 469.59
LEMD, mg	226.50 ± 109.19	323.11 ± 96.82	284.47 ± 109.61
UPDRS-IV, score	7.67 ± 5.01	11.00 ± 3.87	9.67 ± 4.51
KPPS Total, score	48.50 ± 37.37	49.22 ± 18.97	48.93 ± 26.54
BPI-intensity, score	5.38 ± 1.03	4.86 ± 1.50	5.07 ± 1.31
BPI-interference, score	6.33 ± 3.58	5.92 ± 3.13	6.09 ± 3.20
STAI-state, score	23.00 ± 10.04	23.00 ± 11.92	23.00 ± 10.82
STAI-trait, score	28.83 ± 8.42	26.22 ± 12.65	27.27 ± 10.89
BDI, score	17.00 ± 9.32	15.89 ± 11.30	16.33 ± 10.21
TSK-11, score	27.00 ± 7.21	21.00 ± 5.43	23.40 ± 6.68
PCS, score	24.50 ± 12.53	23.44 ± 11.04	23.87 ± 11.22

Abbreviations: BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; KPPS, King's Parkinson's disease Pain Scale; LEDD, Levodopa Equivalent Daily Dose; LEMD, Levodopa Equivalent Morning Dose; PCS, Pain Catastrophizing Scale; STAI, State–Trait Anxiety Inventory; TSK-11, Tampa Scale of Kinesiophobia-11; UPDRS-IV, Unified Parkinson's Disease Rating Scale-Part IV.
[a]*n* (%); Mean ± SD.

3.6 | Adverse Effects

No adverse effects were reported.

4 | Discussion

tDCS has been systematically explored on PD-related pain in patients in the On medication state, showing promising outcomes in pain modulation, perception, sensitivity, and expansion using a daily protocol with 10 sessions [12]. This finding raised the question of whether immediate effects from single sessions could, by themselves, influence pain processing or potentially enhance the effects of dopaminergic medication when paired with the medication's Off state.

The objective of this triple-blinded crossover study was to evaluate the impact of a single session of tDCS applied before the administration of dopaminergic medication on pain modulation, perception, sensitivity, and expansion, in comparison to a sham tDCS session in patients with PD-related pain. Secondarily, we aimed to determine the immediate effect of a single session of tDCS while patients were in the Off state on the same parameters.

Overall, no additional effects to dopaminergic medication were found after the application of active tDCS on CPM, NPRS, GROC, PPT's, or WMH. When administered during the Off state, active tDCS failed to enhance CPM, GROC, PPT's, or WMH. However, a single session of active tDCS, while patients were in the Off state, reduced immediately their pain perception immediately, as measured by the NPRS, compared to sham stimulation.

4.1 | Additional Effect of Active tDCS to Dopaminergic Medication on Pain Measures: Effects at ON State

There is some evidence suggesting that tDCS itself may have effects on dopamine release and activity [58–60], but the intersection of tDCS and dopaminergic medication in immediately enhancing pain processing outcomes for PD-related pain remains unexplored. The present investigation was spurred by the ambiguous role of dopamine in pain mechanisms. On the one hand, dopamine is hypothesized to possess hypoalgesic properties [6, 7]. On the other hand, existing research also suggests that dopamine might actually exacerbate pain

TABLE 3 | Pain outcome measures during OFF (baseline) and ON (post-intervention) states, for the active and sham Transcranial Direct Current Stimulation (tDCS) sessions, by sequence.

	Active-Sham				Sham-Active			
Pain measure	**Active (baseline)[a]**	**Active (post)[a]**	**Sham (baseline)[a]**	**Sham (post)[a]**	**Active (baseline)[a]**	**Active (post)[a]**	**Sham (baseline)[a]**	**Sham (post)[a]**
CPM, kg	0.95 ± 1.17	0.81 ± 1.04	1.04 ± 1.87	2.48 ± 2.95	1.07 ± 0.81	1.04 ± 1.26	0.90 ± 0.64	0.94 ± 1.20
NPRS, points	4.92 ± 2.69	3.17 ± 2.48	3.75 ± 2.62	3.25 ± 2.56	5.50 ± 2.65	1.56 ± 1.49	4.72 ± 2.14	1.67 ± 1.95
Local PPT, kg	2.95 ± 1.67	3.77 ± 2.80	3.20 ± 1.63	3.80 ± 1.66	2.09 ± 1.12	2.84 ± 1.82	2.19 ± 1.39	2.85 ± 2.42
Remote PPT, kg	4.16 ± 1.72	4.62 ± 2.35	3.96 ± 2.01	4.56 ± 2.00	3.47 ± 1.81	4.19 ± 2.27	3.58 ± 2.46	4.01 ± 2.67
WMH, kg	7.10 ± 3.25	8.39 ± 5.09	7.16 ± 3.47	8.35 ± 3.58	5.56 ± 2.77	7.03 ± 3.93	5.88 ± 3.75	6.86 ± 4.84

Abbreviations: CPM, Conditioned Pain Modulation; NPRS, Numeric Pain Rating Scale; PPT, Pain Pressure Threshold; WMH, Widespread Mechanical Hyperalgesia.
[a]Mean ± SD.

in PD patients [61], adversely affecting their quality of life. Moreover, prior studies have not demonstrated a positive impact of dopaminergic medication on CPM responses in PD [9, 61]. The literature on pain sensitivity and expansion, as assessed through pain thresholds, remains heterogeneous regarding dopamine's effects, further complicating our understanding. While some studies found beneficial effects of dopaminergic therapy in raising pain thresholds [6] and nociceptive flexion reflex [7], others suggested no effects on pain thresholds when using pressure, thermal, and current stimuli [62, 63], nor in WMH [64].

Given these mixed findings, we posited that incorporating a neuromodulatory approach like tDCS might elucidate the potential benefits of dopamine on pain. Nevertheless, contrary to the previous results from tDCS administered in the On state [12], we surprisingly found that dopamine, when added to tDCS, did not yield additional benefits in terms of pain modulation, perception, perception of change, sensitivity, or expansion.

Several distinctions between our approach and the previous study might account for the lack of significant changes observed in CPM, NPRS, GROC, PPT's, or WMH in our results. First, given the exploratory nature of our study, the sample size was limited, and therefore a lack of power cannot be ruled out. Second, the earlier study applied 10 tDCS sessions while patients were already in the On state, possibly benefiting from repetitive stimulation [65, 66] and enhanced cortical excitability due to dopaminergic medication as seen in previous experimental studies [67], which may have augmented clinical improvements. Our study, however, explored the effects of one single session tDCS during the Off state followed by the dopaminergic medication intake. While single-session tDCS may induce transient effects, evidence suggests that repeated sessions are more effective in engaging descending pain modulatory systems and producing neuroplastic changes within central networks [66, 68]. Moreover, we could not benefit from that previous cortical excitability increment from dopamine that may have enhanced the effect in the previous trial. This highlights the need to consider session frequency when aiming to modulate endogenous pain control mechanisms and the importance of considering the sequence of administration for the interventions (dopamine—tDCS or tDCS—dopamine).

These findings indicate the need for further research into the interaction between tDCS and dopaminergic medication in PD-related pain management. The complex nature of this interaction requires deeper investigation to optimize therapeutic strategies and could also be mediated by inter-individual variability in both clinical and pain characteristics. It has been reported that clinical factors such as PD severity can modulate the effects of tDCS on both motor and cognitive symptoms [69]. In addition, PD-related pain has been described as comprising multiple pain subtypes (e.g., chronic or fluctuation-related), which could potentially have different neural substrates. Hence, it seems reasonable that individuals with PD exhibiting one or more pain subtypes, or one predominant subtype, might benefit from specific tDCS interventions to a greater extent depending on stimulation parameters such as dose or brain target. Our study was not powered enough to perform such analyses, which

TABLE 4 | Summaries of main effects for each outcome measure for the Linear Mixed-Effects Models, considering the models at ON state (additional effect of tDCS to levodopa intake).

	CPM		NPRS		Local PPT		Remote PPT		WMH	
Predictors	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**
Intercept	0.36	−1.80–2.53	0.97	−0.95–2.89	−0.31	−2.06–1.45	−0.03	−1.52–1.46	−0.78	−3.65–2.09
Treatment	−0.80	−2.06–0.46	−0.64	−1.57–0.29	0.22	−0.65–1.09	0.08	−0.63–0.78	0.33	−1.07–1.74
Period	0.83	−0.43–2.09	0.09	−0.80–0.99	−0.09	−0.97–0.78	0.22	−0.49–0.93	0.23	−1.17–1.63
Sequence	−0.65	−1.91–0.61	−2.03	−3.29 to −0.77	0.32	−0.60–1.24	0.07	−0.73–0.88	0.29	−1.15–1.73
Baseline	0.44	−0.15–1.03	0.56	0.32–0.80	1.34	1.02–1.66	1.05	0.85–1.25	1.21	0.99–1.43
Random effects										
σ^2	2.68		1.36		1.28		0.84		3.31	
τ_{00}	0.00_{ID}		0.63_{ID}		0.00_{ID}		0.12_{ID}		0.00_{ID}	
ICC			0.32				0.12			
N	15_{ID}		15_{ID}		15_{ID}		15_{ID}		15_{ID}	
Observations	30		30		30		30		30	
Marginal R^2/ Conditional R^2	0.186/NA		0.546/0.691		0.731/NA		0.815/0.838		0.820/NA	

Abbreviations: σ^2, mean random effect variance; τ_{00}, random intercept variance; CI, Confidence Interval; Conditional R^2, variance of the fixed and random effects; CPM, Conditioned Pain Modulation; ICC, Intraclass Correlation Coefficient; Marginal R^2, variance of the fixed effects; NPRS, Numeric Pain Rating Scale; PPT, Pain Pressure Threshold; WMH, Widespread Mechanical Hyperalgesia.

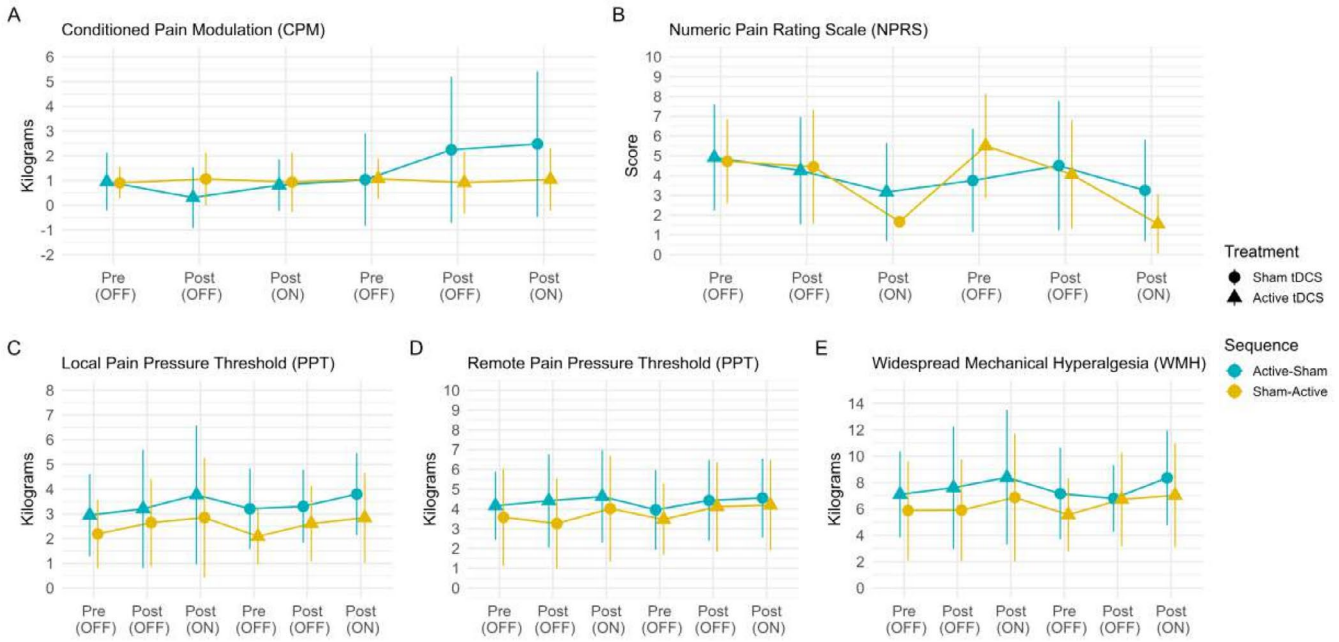

FIGURE 3 | Results of clinical trial. Each plot represents the group-level mean ± SD for each measurement (pre-tDCS in the OFF state, post-tDCS in the OFF state, and post-tDCS in the ON state) and condition (active or sham tDCS). These values are taken from sample statistics. For each plot, conditions were compared using a linear mixed-effects model with the formula y~(1|Participant) + Treatment + Sequence + Period + Baseline. Panels a, b, c, d, and e correspond to results for Conditioned Pain Modulation (CPM), Numeric Pain Rating Scale (NPRS), Local and Remote Pain Pressure Thresholds (PPT), and Widespread Mechanical Hyperalgesia (WMH), respectively. Group mean and standard deviation plots for every clinical outcome measure. TDCS = transcranial Direct Current Stimulation. (A) Group mean and standard deviation plot for Conditioned Pain Modulation (CPM). (B) Group mean and standard deviation plot for Numeric Pain Rating Scale (NPRS). (C) Group mean and standard deviation plot for Local Pain Pressure Threshold (PPT). (D) Group mean and standard deviation plot for Remote Pain Pressure Threshold (PPT). (E) Group mean and standard deviation plot for Widespread Mechanical Hyperalgesia (WMH).

will be essential for advancing our understanding to enhance pain relief and the quality of life for PD patients.

4.2 | Exclusive Effect of tDCS in Off State: Immediate Effects

As the secondary objective, our study represents a unique exploration into the effects of a single session of active tDCS on pain in PD patients in their Off medication state, expanding upon existing literature that predominantly focuses on patients in the On state [12]. Contrary to expectations, we observed no improvements in pain modulation, perception of change, sensitivity, and expansion.

Previous evidence suggests that changes in excitability in the human cortex mediated by tDCS stimulation in M1 may consolidate its effects by D2 receptor activation [60, 70]. As D2 stimulation is affected in low dopaminergic states, it may be a potential mechanism explaining why Off stimulation did not have clear effects on pain variables.

The evidence suggesting that tDCS alone could enhance endogenous dopamine release in the ventral striatum following stimulation of the dorsolateral prefrontal cortex [58] raises questions about whether this effect is specific to the stimulation site or if the hypothetical release is insufficient to induce enhancements in the cortico–nigral pathway.

Despite this, we did observe an immediate improvement in pain perception after active tDCS as assessed by the NPRS, diverging from tDCS during the On state, where no such immediate effect was noted using the KPPS, being notable 15 days later [12]. This discrepancy may be due to the differing methodologies of pain assessment. The KPPS evaluates the intensity and frequency of 14 types of pain over the previous 2 weeks, while the NPRS assesses pain intensity at a specific moment, making it potentially more suitable for observing the immediate impact of tDCS. In fact, in our study, immediate pain relief might be associated with momentaneous counteracting cortical excitability reduction observed in PD's Off stages ([71, 72]). It remains to be determined whether such immediate analgesic effects could accumulate or persist with repeated sessions [66]. Studies using other neuromodulation techniques, like repetitive Transcranial Magnetic Stimulation, have also shown success in alleviating PD-related pain as assessed by NPRS [73].

The discrepancy between the improvement in subjective pain perception and the absence of changes in pain processing variables may be due to differential sensitivity to acute neuromodulation. The selective NPRS reduction may reflect tDCS-induced M1 modulation of affective pain dimensions [74], while mechanisms such as CPM rely on brainstem–spinal cord connectivity, which may be less responsive to a single session. This suggests that activating descending inhibitory pathways and inducing neuroplastic changes may require repeated stimulation over time. Additionally, the limited sample size may

TABLE 5 | Pain outcome measures during OFF (baseline) and OFF (post-intervention) states, for the active and sham Transcranial Direct Current Stimulation (tDCS) sessions, by sequence.

	Active-Sham				Sham-Active			
Pain measure	**Active (Baseline)**	**Active (Post)**	**Sham (Baseline)**	**Sham (Post)**	**Active (Baseline)**	**Active (Post)**	**Sham (Baseline)**	**Sham (Post)**
CPM, kg	0.95 ± 1.17	0.31 ± 1.22	1.04 ± 1.87	2.24 ± 2.95	1.07 ± 0.81	0.91 ± 1.26	0.90 ± 0.64	1.06 ± 1.07
NPRS, points	4.92 ± 2.69	4.25 ± 2.72	3.75 ± 2.62	4.50 ± 3.27	5.50 ± 2.65	4.06 ± 2.74	4.72 ± 2.14	4.44 ± 2.88
Local PPT, kg	2.95 ± 1.67	3.20 ± 2.39	3.20 ± 1.63	3.30 ± 1.48	2.09 ± 1.12	2.61 ± 1.53	2.19 ± 1.39	2.65 ± 1.78
Remote PPT, kg	4.16 ± 1.72	4.41 ± 2.36	3.96 ± 2.01	4.43 ± 2.04	3.47 ± 1.81	4.11 ± 2.26	3.58 ± 2.46	3.26 ± 2.27
WMH, kg	7.10 ± 3.25	7.61 ± 4.64	7.16 ± 3.47	6.79 ± 2.54	5.56 ± 2.77	6.72 ± 3.56	5.88 ± 3.75	5.91 ± 3.85

Note: Mean ± SD.
Abbreviations: CPM, Conditioned Pain Modulation; NPRS, Numeric Pain Rating Scale; PPT, Pain Pressure Threshold; WMH, Widespread Mechanical Hyperalgesia.

have contributed to Type II errors, potentially obscuring subtle but meaningful effects.

The observed immediate improvement in pain perception opens avenues for further research. It underscores the importance of considering medication stages, session frequency, and the selection of appropriate pain assessment scales in future investigations into tDCS's therapeutic potential for pain management in PD.

4.3 | Strengths and Limitations

Our study is subject to several limitations that warrant mention. First, although correctly calculated, the modest sample size of 15 participants restricts the external validity of our findings, making it challenging to generalize the results to a broader population. However, our study provides preliminary data for future large-scale trials that could use our detected effect sizes to estimate required sample sizes (e.g., see Tables S5 and S10 for standardized effect sizes across outcome measures). Moreover, there was an imbalance in the randomization sequences (active-sham or sham-active); however, subsequent analyses indicated that this did not significantly impact the results. Besides, the investigation was limited to a single session of treatment, chosen to assess the immediate effects of tDCS in the Off state and following dopaminergic medication intake, which may not reflect longer-term outcomes. Another potential limitation is the specific target region within the brain where tDCS is applied, given that previous studies have stimulated different locations [58]; the consequences of applying it to alternative brain areas remain unknown. It is also worth noting to mention that in our study, the evaluation of pain in the On state occurred about 60–90 min after tDCS application, and this may have prevented us from capturing the initial peak effect of a single tDCS session, which is theorized to occur immediately and return to baseline gradually within 120 min [75]. Additionally, this timing may have attenuated potential synergistic effects between tDCS and dopaminergic medication, which might have been more pronounced if levodopa had been administered immediately after stimulation. Future studies using separate sessions could help disentangle these effects more precisely, though such designs also entail increased burden for patients and a higher risk of dropout. Furthermore, the inability to standardize the dopaminergic and adjunct medication across all participants, as each participant requires its own dose to enter the On state, introduces variability, as we could not guarantee uniform interactions between tDCS and the various medications, potentially influencing the study's outcomes. However, because our study used a within-participants design, the potential effects of this variability would have been minimized compared to between-participants designs. Future RCTs using parallel group designs would require accounting for LEDD and other important clinical characteristics of PD in their analyses. As well, individual differences in baseline cortical excitability [26] and neuroanatomy such as skull thickness, cerebrospinal fluid volume, and cortical folding [76, 77] may have influenced current distribution and response to stimulation, adding further variability. Lastly, adverse effects were assessed only using the CRQ immediately after stimulation, without additional follow-up, which may have missed delayed-onset symptoms, particularly relevant in PD patients.

TABLE 6 | Summaries of main effects for each outcome measure for the Linear Mixed-Effects Models, considering the models at post-intervention (exclusive effect of tDCS).

	CPM		NPRS		Local PPT		Remote PPT		WMH	
Predictors	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**	**Estimates**	**95% CI**
Intercept	0.15	−2.03–2.33	0.55	−1.66–2.77	−0.31	−1.39 to 0.76	−0.97	−1.83 to −0.10	−0.68	−3.29–1.94
Treatment	−1.06	−2.33–0.21	−1.28	−2.48 to −0.08	0.14	−0.39–0.67	0.37	−0.06–0.80	1.01	−0.27–2.29
Period	0.84	−0.43–2.12	0.12	−1.05–1.30	−0.06	−0.59–0.47	0.60	0.17–1.03	0.13	−1.15–1.41
Sequence	−0.28	−1.55–0.99	−0.89	−2.08 to 0.30	0.47	−0.09–1.03	−0.17	−0.60–0.27	0.54	−0.78 –1.85
Baseline	0.39	−0.21 –0.98	0.99	0.74–1.23	1.17	0.97–1.36	1.06	0.95–1.17	1.01	0.80–1.21
Random effects										
σ^2	2.72		2.32		0.48		0.31		2.75	
τ_{00}	0.00_{ID}		0.00_{ID}		0.00_{ID}		0.00_{ID}		0.00_{ID}	
N	15_{ID}		15_{ID}		15_{ID}		15_{ID}		15_{ID}	
Observations	30		30		30		30		30	
Marginal R^2/ Conditional R^2	0.177/NA		0.704/NA		0.843/NA		0.934/NA		0.791/NA	

Abbreviations: σ^2, mean random effect variance; τ_{00}, random intercept variance; CI, Confidence Interval; Conditional R^2, variance of the fixed and random effects; CPM, Conditioned Pain Modulation; Marginal R^2, variance of the fixed effects; NPRS, Numeric Pain Rating Scale; PPT, Pain Pressure Threshold; WMH, Widespread Mechanical Hyperalgesia.

4.4 | Clinical Implications

These findings suggest that single-session tDCS may serve as a rapid, rescue-like intervention for alleviating pain during Off-medication states in patients with PD. However, given the lack of significant changes in descending pain modulation markers, multiday stimulation protocols appear necessary to induce more stable neuroplastic and clinical effects. Moreover, individual variability in response to stimulation—particularly in relation to medication timing—underscores the need for personalized treatment strategies. Optimizing the temporal relationship between tDCS application and dopaminergic intake may enhance synergistic effects and improve therapeutic efficacy in pain management.

5 | Conclusion

In conclusion, a single session of active tDCS targeting the M1 may immediately reduce pain perception in PD patients during the Off state, yet it does not enhance endogenous pain modulation, pain sensitivity, or pain expansion. Additionally, the adjunctive use of dopaminergic medication does not confer additional benefits to active tDCS in pain processing, although it is effective in controlling motor symptoms, suggesting pathways different from dopaminergic ones in pain regulation in PD. Future investigations should delve into the potential synergistic effects of combining tDCS with dopaminergic medication for more effective pain management in PD patients.

Author Contributions

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Ethics Statement

Ethical approval was obtained from Hospital Universitario 12 de Octubre (Madrid, Spain, N°CEIm: 23/032) and the study was conducted according to the Declaration of Helsinki [20].

Consent

Written informed consent was obtained and signed from all participants prior to enrollment.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/ja4cp/files/osfstorage/67dac43c8dd8524c6b5224b8, reference number https://doi.org/10.17605/OSF.IO/JA4CP.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Unified Parkinson's Disease Rating Scale (UPDRS) scores during OFF and ON states, for the active and sham sessions. **Table S2:** Pain outcome measures during OFF (baseline) and ON (post-intervention) states, for the active and sham Transcranial Direct Current Stimulation (tDCS) sessions, by participant. **Table S3:** Differences between active and sham Transcranial Direct Current Stimulation (tDCS) sessions at post-intervention (ON state) as group averages, by sequence. **Table S4:**. ANOVA table of main effects for each outcome measure, considering the models at ON state (additional effect of tDCS to levodopa intake). **Table S5:**. Effect size between active and sham Transcranial Direct Current Stimulation (tDCS) for each outcome measure at ON state (after levodopa intake). **Table S6:**. Summaries of the Linear Mixed-Effects Models for the Global Rating of Change Score (GROC). **Table S7:**. Pain outcome measures at baseline (pre-intervention) and post-intervention, both during OFF state, for the active and sham Transcranial Direct Current Stimulation (tDCS) sessions, by participant. **Table S8:**. Differences between active and sham Transcranial Direct Current Stimulation (tDCS) sessions at post-intervention (OFF state) as group averages, by sequence. **Table S9:**. ANOVA table of main effects for each outcome measure, considering the models at post-intervention (exclusive effect of tDCS). **Table S10:**. Effect size between active and sham Transcranial Direct Current Stimulation (tDCS) for each outcome measure at post-intervention (during OFF state, immediately after tDCS). **Table S11:**. Cook's distance for each observation, according to the models assessing the additional effect of Transcranial Direct Current Stimulation (tDCS) to levodopa intake. **Table S12:**. Summaries of main effects for each outcome measure for the Linear Mixed-Effects Models, considering the models at ON state (additional effect of tDCS to levodopa intake) after removing outliers based on Cook's distance. **Table S13:**. Cook's distance for each observation, according to the models assessing the exclusive effect of Transcranial Direct Current Stimulation (tDCS). **Table S14:**. Summaries of main effects for each outcome measure for the Linear Mixed-Effects Models, considering the models at post-intervention (exclusive effect of tDCS), after removing outliers based on Cook's distance. **Table S15:**. Cook's distance for the Linear Mixed-Effects Models for the Global Rating of Change Score (GROC). **Table S16:**. Summary of the Linear Mixed-Effects Models for the Global Rating of Change Score (GROC) from post-intervention to ON, after removing outliers based on Cook's distance.