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No Effect of a Single Session of Anodal Transcranial Direct Current Stimulation on Exercise-Induced Hypoalgesia in Knee Osteoarthritis: A Randomized Cross-Over Trial

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ABSTRACT

Background: Exercise induces short-term pain relief (exercise-induced hypoalgesia, EIH), but this response is often blunted in people with knee osteoarthritis (OA). Transcranial direct current stimulation (tDCS) has been proposed as a potential enhancer of EIH.

Objective: This study aimed to determine whether a single session of 2-mA anodal tDCS applied for 20 minutes over the contralateral primary motor cortex augments the exercise-induced hypoalgesic response to isometric quadriceps exercise in individuals with knee OA.

Materials and Methods: In this double-blind randomized cross-over trial, 27 participants with knee OA completed two experimental sessions (active anodal tDCS + exercise; sham tDCS + exercise) in counterbalanced order. Pressure pain thresholds (PPTs at the knee and forearm), resting knee pain, and evoked knee pain during stepping were assessed pre- and post intervention. Linear mixed models compared pre- and postexercise changes between active and sham conditions. Blinding success was evaluated using Bang's blinding index.

Results: Both sessions produced EIH (knee PPT increased pre-to-post; all $p \leq 0.001$). Between active and sham conditions, there were no significant differences for knee PPT (mean difference 0 kPa [95% CI −50 to 40], $p = 0.82$), forearm PPT (−20 kPa [−60 to 30], $p = 0.45$), resting knee pain (1/100 [−13 to 15], $p = 0.89$), or evoked knee pain (1/100 [−7 to 8], $p = 0.14$). Blinding was successful, and no adverse events were reported.

Conclusions: These findings indicate that a single session of anodal tDCS does not augment the immediate EIH response to isometric quadriceps exercise in people with knee OA.

Perspective: This randomized cross-over trial found that anodal tDCS did not enhance EIH in people with knee OA. These findings suggest that a single session of anodal tDCS does not meaningfully augment the immediate exercise-induced hypoalgesic response in individuals with knee OA.

Clinical Trial Registration: The Australian New Zealand Clinical Trials Registry number for the study is ACTRN12621000787886, registered July 1, 2021, prospectively.

Keywords: Clinical trial, exercise-induced hypoalgesia, knee osteoarthritis, pain, transcranial direct current stimulation

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of persistent musculoskeletal pain, with considerable personal and societal burden.[1] Exercise is recommended as first-line treatment for knee OA by international evidence-based guidelines;[2,3] however, substantial variability exists in individual responses.[4–6]

One of the proposed mechanisms underlying exercise analgesia is exercise-induced hypoalgesia (EIH), a short-term reduction in pain sensitivity after exercise.[7,8] Although EIH is consistently

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observed in healthy individuals, responses in people with chronic pain, including knee OA, are mixed[8] and may include hyperalgesia. Notably, in people with knee OA, an impaired EIH response has been associated with flares in pain,[9–11] and impaired long-term pain relieving effects of exercise.[12] Although EIH is commonly used to characterize endogenous pain modulation after exercise, the extent to which short-term changes in pain sensitivity translate to sustained clinical improvements in people with knee OA remains uncertain.[8] Accordingly, EIH is best conceptualized as a mechanistic marker of pain modulatory function rather than a direct surrogate of clinical pain outcomes.

Despite the potential importance of EIH in the management of knee OA pain, studies aiming to enhance EIH are sparse. Transcranial direct current stimulation (tDCS) has emerged as a promising, noninvasive intervention, with evidence suggesting it may reduce knee OA pain when applied over the primary motor cortex (M1), particularly in combination with exercise.[13–18] In knee OA, most of the tDCS studies indicating reductions in clinical pain or improvements in pain modulation have used multisession stimulation protocols, most commonly delivering 2-mA anodal stimulation over M1 across ≥five sessions.[13–19] In contrast, the short-term effects of a single session of tDCS remain less well characterized. Notably, most tDCS protocols showing clinical benefit in knee OA have been delivered in isolation, without any concurrent or subsequent exercise, and none have specifically combined stimulation with sustained isometric contractions,[15,16,18,19] limiting direct comparison with exercise-coupled EIH paradigms.

tDCS and exercise have been proposed to independently reduce pain through opioidergic mechanisms and increased descending inhibition of nociception.[8,20–22] However, evidence to date regarding the ability of tDCS to modulate EIH is limited and somewhat inconsistent. In an experimental pain model, Borovskis et al[23] reported that 1-mA anodal tDCS accelerated the onset of EIH during isometric exercise. More recently, Lewis et al[24] conducted a larger cross-over trial in healthy adults and found that 2-mA anodal tDCS did not enhance EIH beyond isometric exercise alone and produced no independent hypoalgesic effects. However, the immediate effects of tDCS have not been trialed in a population with clinical pain such as knee OA, in whom endogenous opioid function,[25] descending inhibition of nociception,[26] and EIH[27,28] are often impaired.

Thus, the aim of this study was to evaluate whether a single session of 2-mA anodal tDCS applied over the contralateral M1 could enhance the EIH response to isometric quadriceps exercise in individuals with knee OA. We incorporated clinically meaningful outcomes of resting and evoked knee pain in addition to traditional pain sensitivity measures. It was hypothesized that compared with sham tDCS, 2-mA anodal tDCS would augment the exercise-induced hypoalgesic response, reflected by larger pre- to postexercise reductions in pain sensitivity and clinical pain intensity.

MATERIALS AND METHODS

Design and Participants

This double-blind randomized cross-over trial was conducted between September and December 2022. The 2010 Consolidated Standards of Reporting Trials (CONSORT) statement[29] and 2019 CONSORT of Extension to Randomised Crossover Trials[30] were used as guidelines for reporting. All procedures were approved by the Health and Disability Ethics Committee (21STH128) and Auckland University of Technology Ethics Committee (21/242), and written informed consent was obtained from participants before testing. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000787886).

Participants were recruited through online and paper advertisements and from existing research data bases. In addition, paper advertisements were left with local knee surgeons, rheumatologists, and physiotherapy clinics in the Auckland region of Aotearoa, New Zealand. Participants were included if they were adults aged ≥45 years, met The National Institute for Health and Care Excellence (NICE) clinical criteria for the diagnosis of knee OA, had ongoing knee pain for ≥three months, and had an average knee pain intensity of ≥3/10 on a numerical pain rating scale (NPRS) in the last week at the time of screening, where 0 = "no pain" and 10 = "worst pain imaginable."

Participants were excluded if they had an inability to speak or write English, medical conditions preventing safe participation in physical activity or tDCS, an inability to climb two flights of stairs, ever had a total knee replacement, a recent history of lower limb resistance training, any other form of arthritis, a history of musculoskeletal pain or injury in the lower limb (other than OA) or knee surgery in the past six months, any neurologic condition, a current diagnosis of a major psychiatric disorder, or any cognitive impairment.

Sample Size

A total of 27 participants were required to achieve a probability of 80% that the study would detect a difference in EIH between active and sham tDCS at a one-sided 0.05 significance level, with at least a moderate effect size of $d = 0.5$. This estimate was informed by prior experimental work evaluating the effects of a single session of anodal tDCS on endogenous pain modulation. Specifically, Flood et al[22] reported a large effect ($d = 0.89$) of active vs sham tDCS on conditioned pain modulation (CPM), a construct that is believed to share at least partially overlapping mechanisms with EIH.[8] In the absence of prior studies evaluating tDCS effects on EIH in people with knee OA, an effect size of $d = 0.5$ was therefore selected as a conservative estimate, particularly given the expected interindividual variability in EIH responses in clinical pain populations. A one-sided test was deemed appropriate given the clear directional hypothesis and the specific aim of determining whether active tDCS was superior to sham.[31]

Randomization, Allocation Concealment, and Blinding

The order of interventions (active vs sham tDCS) was randomized for each participant in a 1:1 ratio using a computer-generated randomization schedule (sealedenvelope.com) with permuted blocks of two and four. An independent researcher distributed and stored the randomization sequence in sealed, opaque envelopes to maintain allocation concealment. All participants and outcome assessors were blinded to intervention order. Participants were told that the trial would "compare real and fake brain stimulation with exercise on knee osteoarthritis pain." The therapist delivering the interventions was blinded to whether active or sham stimulation was applied. Two different tDCS units (labeled A and B) were preprogrammed to deliver either active or sham stimulation by another investigator uninvolved in participant recruitment, screening, or testing. After completing the baseline assessments for each participant, the therapist delivering the intervention opened an opaque sealed envelope to see which unit (A or B) to

use at the first visit. The statistician responsible for data analysis was blind to intervention order.

Procedures

The experimental procedures are outlined in Figure 1. Participants attended two laboratory sessions ≥seven days apart ("visit 1" and "visit 2"). Participants were instructed to abstain from caffeine and analgesic medications for ≥12 hours before each testing session, to avoid vigorous exercise and alcohol for 24 hours beforehand, and to refrain from nicotine use for ≥two hours before testing. Each visit took approximately two hours. During visit 1, participants provided demographic and clinical data and completed questionnaires regarding their pain, mental health, and physical function. These included the Brief Pain Inventory,[32] Hospital Anxiety and Depression Scale,[33] Lower Limb Tasks Questionnaire,[34] Pain Catastrophizing Scale,[35] and the Tampa Scale of Kinesiophobia.[36]

To allow standardization of exercise intensity during the evaluation of EIH, at the beginning of each visit, participants completed an assessment of their maximum voluntary isometric contraction (MVIC) of the quadriceps muscle group. The index knee (or most painful knee for those with bilateral OA) was secured to a Biodex Multi-Joint System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY). Hip flexion was fixed to 85° and knee flexion fixed to 90°. A standardized warm-up of four 5-second isometric quadriceps contractions at 25%, 50%, 50%, and 75% of perceived maximum effort was performed, followed by three 5-second maximum effort voluntary contractions with a 30-second rest period between contractions. Consistent verbal encouragement was given for all contractions, and MVIC was taken as the peak torque (Nm) produced during any of the maximum effort contractions. After MVIC testing and a 15-minute rest period, participants were familiarized with the upcoming EIH testing procedure, to obtain pain expectancy scores. Participants were asked to rate their familiar knee pain (0–100 on the NPRS) and told that they would soon be instructed to maintain a target torque of 25% of their MVIC for a maximum of 5 minutes or until failure. They were then asked to practice holding a target torque of 25% of MVIC for 10 seconds and asked to rate (0–100 on the NPRS) what they expected their familiar knee pain to be if they were to hold the same level of contraction to failure or 5 minutes.

Baseline measures of evoked knee pain, pressure pain thresholds (PPTs), and resting joint pain were then obtained. Participants then received 20 minutes of tDCS (active/sham) and performed an assessment of blinding success. The isometric exercise protocol was then undertaken, and evoked pain, resting pain, and PPTs were reassessed immediately afterward to enable measures of EIH.

Visit 2 was the same as visit 1, excluding questionnaire-based data, but participants received the cross-over active/sham tDCS intervention, and the outcome measures were repeated (Fig. 1). A minimum seven-day washout period between visits was implemented to avoid any potential carry-over effects from the intervention.[37,38]

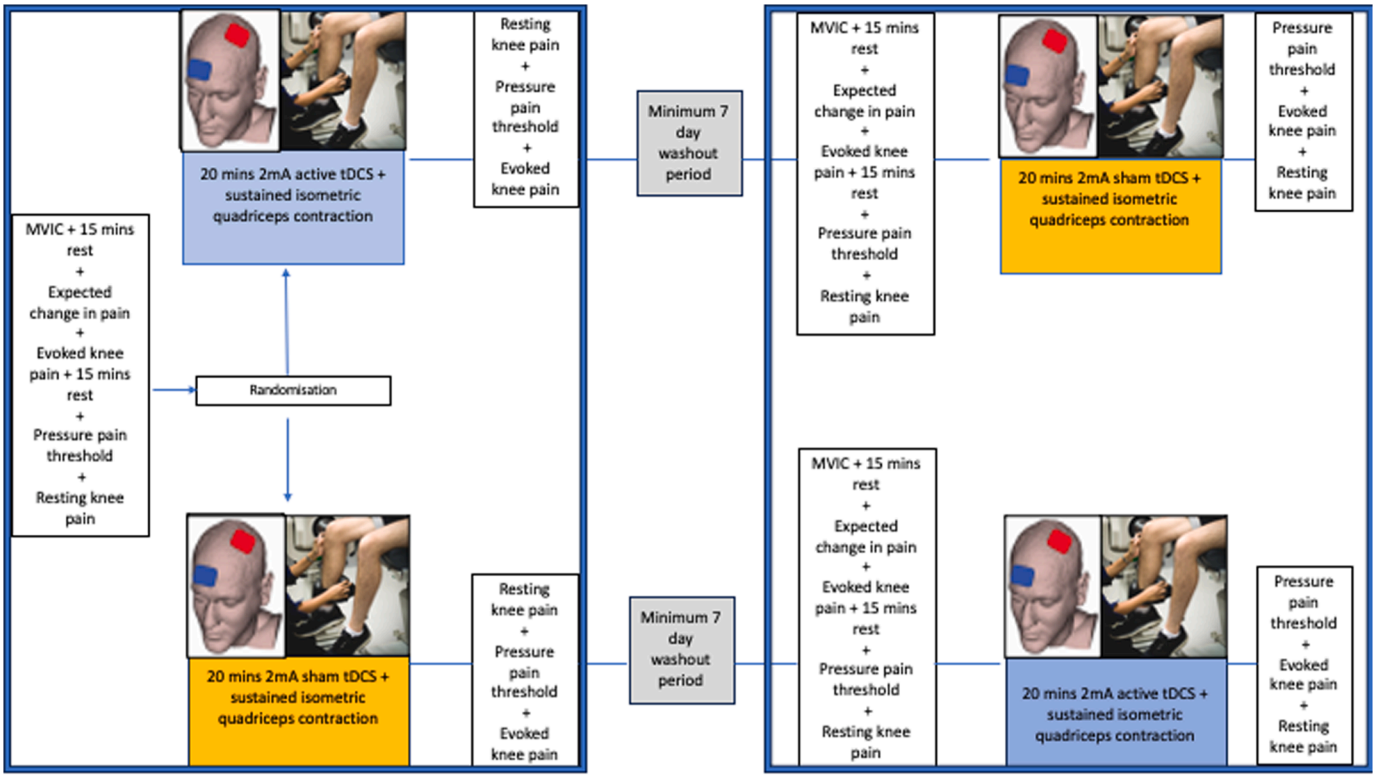

Figure 1. Experimental procedures. After baseline measurements, participants were randomized to receive 20 minutes of active (intervention) or sham tDCS (control). After tDCS, EIH was quantified by repeating measurements of PPT, evoked knee pain, and resting knee pain after performing a sustained isometric quadriceps contraction at 25% of (MVIC) for 5 minutes, or until failure. After a minimum seven-day washout period, participants returned and performed an identical testing session but with the alternative tDCS protocol (active/sham). [Color figure can be viewed at www.neuromodulationjournal.org]

Interventions (2-mA Active and Sham tDCS)

Participants were comfortably seated in the dynamometer chair while receiving tDCS and were asked to remain quiet for the duration of the intervention. During the active tDCS session, participants received 20 minutes of 2-mA anodal stimulation, which was applied using an HDCell (MagStim Co, Whitland, UK) and 7 × 5 cm electrodes (0.057 mA/cm^2). Anodal tDCS was delivered at 2 mA, an intensity commonly used in knee OA studies and shown to induce neuromodulatory effects, although effective responses also have been reported across a range of stimulation intensities.[39] The electrode sponges were soaked in saline solution before application, and the skin was wiped with alcohol preparation pads to induce uniform erythema across all participants.[40] These procedures additionally facilitated blinding at the 2-mA intensity, which was required owing to the deep location of the leg representation in the motor cortex[41] and the desire to facilitate consistent effects on cortical excitability.[42,43] The anode was placed over the C3 or C4 scalp location according to the International 10–20 Electroencephalogram.

system,[44] contralateral to the affected knee. The cathode was placed over the contralateral supraorbital region. Stimulation intensity was ramped up to 2 mA over 30 seconds, applied for 20 minutes, and then ramped down to 0 mA over 30 seconds.

In the sham tDCS session, participants received an identical intervention as the active tDCS session except that stimulation intensity was ramped up to 2 mA over 30 seconds and then immediately ramped down to 0 mA over 30 seconds to provide the initial itching sensation.[45] Before the first session, participants were informed that they might or might not perceive any sensation during the application of tDCS. The screen display on the tDCS unit was identical across active and sham sessions.

In both the active and sham sessions, participants watched the same nature documentary (without narration) to maintain alertness and control arousal during the stimulation period, thereby minimizing state differences in brain excitability due to visual input.[46–48] Immediately after stimulation, to assess blinding success, participants were asked "Do you think you received real brain stimulation, fake brain stimulation, or are you not sure?"[49,50]

Isometric Exercise

Immediately after tDCS, to induce EIH, a single submaximal isometric contraction of the quadriceps at a target torque of 25% of MVIC was performed using the Biodex dynamometer. Participants were positioned sitting, with hip flexion fixed at 85° and 90° knee flexion, and were instructed to maintain the target torque until failure or to a maximum of 5 minutes. Failure was defined as the inability to sustain 25% MVIC for ≥5 seconds. Continuous visual feedback of their quadriceps torque was displayed on a computer screen placed directly in front of the participant. During the isometric contraction, a rating of perceived exertion (RPE) on Borg's 6-to-20 scale,[51] with 6 defined as "no exertion at all" and 20 as "maximal exertion," was obtained every 30 seconds. Participants were given consistent verbal encouragement to ensure that true contraction failure or the 5-minute maximum time was reached. If contraction failure occurred, the time to failure (in seconds) was recorded. After this, participants were asked to rate their maximum knee pain during the isometric contraction on a scale from 0 "no pain" to 100 "worst pain imaginable."

Primary Outcome Measures

The primary outcome measures for this study were the change in PPTs from immediately before to immediately after the intervention (active tDCS plus exercise or sham tDCS plus exercise). Before the intervention, PPTs were assessed at two sites, in a random order: at the medial joint line of the index knee and remotely at the volar surface of the contralateral forearm. The same test-site order was used for postexercise measurement of PPTs. PPTs were assessed using a handheld pressure algometer (SbMedic, Solna, Sweden) with a 1-cm rounded tip and a ramping rate of 30 kpa/s. Participants were instructed to press a button at the moment they first experienced any pain from the probe, and the pressure achieved in kPa was recorded. The average of three PPT measurements was recorded for each site. Because there is little consensus whether to report EIH as the absolute (in kPa) or relative (ratio or percentage) change in PPT from pre- to post exercise, and both are frequently used in the literature,[52–54] we chose to report and analyze both absolute and relative changes in PPTs at both local (knee) and remote (forearm) sites. For relative measures, postexercise PPT was expressed as a ratio of preexercise PPT for each individual at each site, such that values >1.0 reflect an increase in PPT (hypoalgesia) after exercise whereas values <1.0 reflect decreased PPTs (hyperalgesia).[55]

Secondary Outcome Measures

Secondary outcomes were changes in resting knee pain intensity and evoked knee pain intensity through the Staircase-Evoked Pain Procedure (StEPP).[56] These assessments also were performed before and after the exercise intervention. Resting knee pain was assessed in sitting, with the knee fixed at 90° of flexion in the dynamometer arm, using a 0-to-100–point NPRS. Evoked pain intensity was measured on the same 0-to-100 NPRS immediately before and after completing the StEPP, which comprised stepping up and down onto a 20-cm–high platform 24 times. To ensure consistency in StEPP performance across time and participants, the test was always started on the index knee, and the left and right limb was alternated between each up/down cycle. Participants were instructed to use their normal gait for completing this task and were encouraged to complete the task despite increasing pain, without stopping. For safety reasons, participants were allowed to use their hands to steady themselves on the back of the Biodex chair if needed but were otherwise asked to complete the StEPP without support. The time taken to complete the StEPP was recorded in seconds. Evoked pain was defined as the change in pain (0–100 NPRS) from before to immediately after completing the StEPP.

A fixed order of outcome measure testing was used for all participants to ensure that, as much as possible, changes in outcome measures reflected the effects of the intervention (active/sham tDCS plus exercise), rather than altered pain sensitivity induced by measurement of other outcomes. The MVIC was performed before baseline pain assessments, followed by a standardized 15-minute rest period to minimize any short-term effects on pain sensitivity.[57] Baseline outcome measures were then assessed in the following order: evoked knee pain (StEPP test), PPTs, and resting knee pain. This order was selected to allow postintervention changes in PPT to be attributed to the intervention itself rather than the combined effects of exercise and

repeated joint loading. Immediately after the intervention, outcomes were assessed in the order of resting knee pain, PPTs, and evoked knee pain (StEPP test).

Adverse Events

Adverse events were defined as any untoward or undesirable medical occurrence during or within 24 hours of the intervention, regardless of whether it was considered causally related. Severity was classified as mild (no limitation of activity), moderate (some limitation of activity), or severe (preventing normal activities or requiring medical attention). Relationship to the intervention was rated as related, possibly related, or unrelated. Increases in resting knee pain were monitored for all participants. An increase of ≥20 points on the 0-to-100 NPRS from pre- to post intervention was considered clinically important and was classified as an adverse event.[58]

Statistical Analysis

Descriptive statistics were used to summarize participant characteristics and exercise-related variables. Continuous data are presented as mean (SD) or median (interquartile range), as appropriate. Isometric contraction force, maximum knee pain during the isometric exercise, and ratings of perceived exertion were collected to characterize the exercise task and confirm comparable exposure across sessions, and are therefore reported descriptively only.

The primary outcome was the change in PPT from pre- to post intervention at the knee and forearm. Secondary outcomes included changes in resting knee pain and evoked knee pain. Absolute change scores (post–pre) were used as the dependent variables in all inferential analyses, with baseline values incorporated into the models. Relative changes are presented descriptively to aid interpretation only. Linear mixed-effects regression models were used to evaluate differences between conditions (active tDCS + exercise vs sham tDCS + exercise), with baseline outcome values and stimulation condition included as fixed effects and participant included as a random intercept to account for within-participant correlations arising from the cross-over design. An identity covariance structure was assumed.

To satisfy CONSORT extension recommendations for cross-over trials, potential carry-over, period, and sequence effects were evaluated by including Group × Session interaction terms and by inspection of outcome patterns across sessions before final model specification. No evidence of carry-over, period, or sequence effects was observed for the primary outcomes, and all participants were therefore included in the final models. For PPT outcomes, the mean of three repeated trials at each site and timepoint was used in all analyses. This approach was specified a priori to improve measurement reliability and reduce within-session variability, and was applied consistently across participants and conditions.

Model diagnostics included visual inspection of residual plots to assess normality and homogeneity of variance. Mean differences across sessions and mean scores for each session are reported along with their 95% CIs and *t*-, *p*-values. Between-session effect sizes for EIH are presented as the mean difference divided by the pooled SD and interpreted according to Cohen's criteria of 0.2 = small, 0.5 = moderate, and 0.8 = large.[59]

Blinding was assessed with Bang's blinding index[49] for each treatment arm. Zero denoted random guessing at the chance level (50%). A positive value denoted the ratio of participants who correctly guessed their treatment arm, and a negative value denoted the ratio of participants who incorrectly guessed the opposite arm. Values between −0.2 and 0.2 can be considered successful blinding.[50]

Data were analyzed in the R environment for statistical computing[60–62] and SPSS version 25 (IBM Corp, Armonk, NY). Any *p*-value <0.05 was considered significant.

RESULTS

Participant Characteristics

A total of 34 participants were screened for eligibility, of whom seven (21%) were excluded, leaving 27 participants (79%) (15 women, 12 men) with a mean (± SD) age of 66 years (±10) were recruited (Fig. 2 and Table 1). Baseline characteristics were similar in the participants randomized to receive active tDCS first to those in the participants receiving sham tDCS first (Table 1), although those receiving sham stimulation first tended to be older, with a longer disease duration, and were more likely to be taking pain medications. All participants completed all the experimental procedures, with no adverse events reported.

Bang's blinding index was 0.12 in the active tDCS session and −0.04 in the sham tDCS session, indicating successful participant blinding.[50] Exercise and task characteristics were similar across the active and sham tDCS sessions (Table 2). Between-condition comparisons were not performed for isometric contraction force, maximum knee pain during exercise, ratings of perceived exertion, or StEPP time to completion because the study was not powered to detect differences in these outcomes. These data are therefore reported descriptively only.

Primary Outcomes

Analysis of the absolute change in PPT revealed no significant differences between the active tDCS and sham tDCS sessions at the knee (mean difference 0 kPa [95% CI −50 to 40 kPa]; $p = 0.82$, $d = 0$) or the forearm (mean difference −20 kPa [95% CI −60 to 30 kPa]; $p = 0.45$, $d = -0.19$) (Table 3).

During both sessions, a significant local EIH response was observed at the knee, with an increase in PPTs from pre- to post intervention using both absolute and relative measures (all $p \leq 0.001$). Despite this, there was notable interindividual variability in the magnitude of the EIH response after both the active and sham tDCS interventions (Fig. 3). A remote EIH response at the forearm was only observed during the sham session ($p = 0.008$) (Table 3).

Secondary Outcomes

There was no significant between-session difference in the pre- to postintervention change in resting pain (mean difference 1 [95% CI −13 to 15]; $p = 0.89$, $d = 0.03$). Notably, resting pain increased in both sessions (active tDCS mean increase: 12/100 [95% CI 2–22]; $p = 0.02$) and (sham tDCS mean increase: 11/100 [95% CI 1–21]; $p = 0.03$) from pre- to post intervention.

Moreover, there was no significant between-session difference in the pre- to postintervention change in evoked pain (mean difference 1 [95% CI −7 to 8]; $p = 0.14$, $d = 0.05$). However, evoked pain decreased from pre- to post intervention in both sessions (active tDCS mean change: −6/100 [95% CI −12 to −1]; $p = 0.03$) and (sham tDCS mean change: −7/100 [95% CI −12 to −1]; $p = 0.02$).

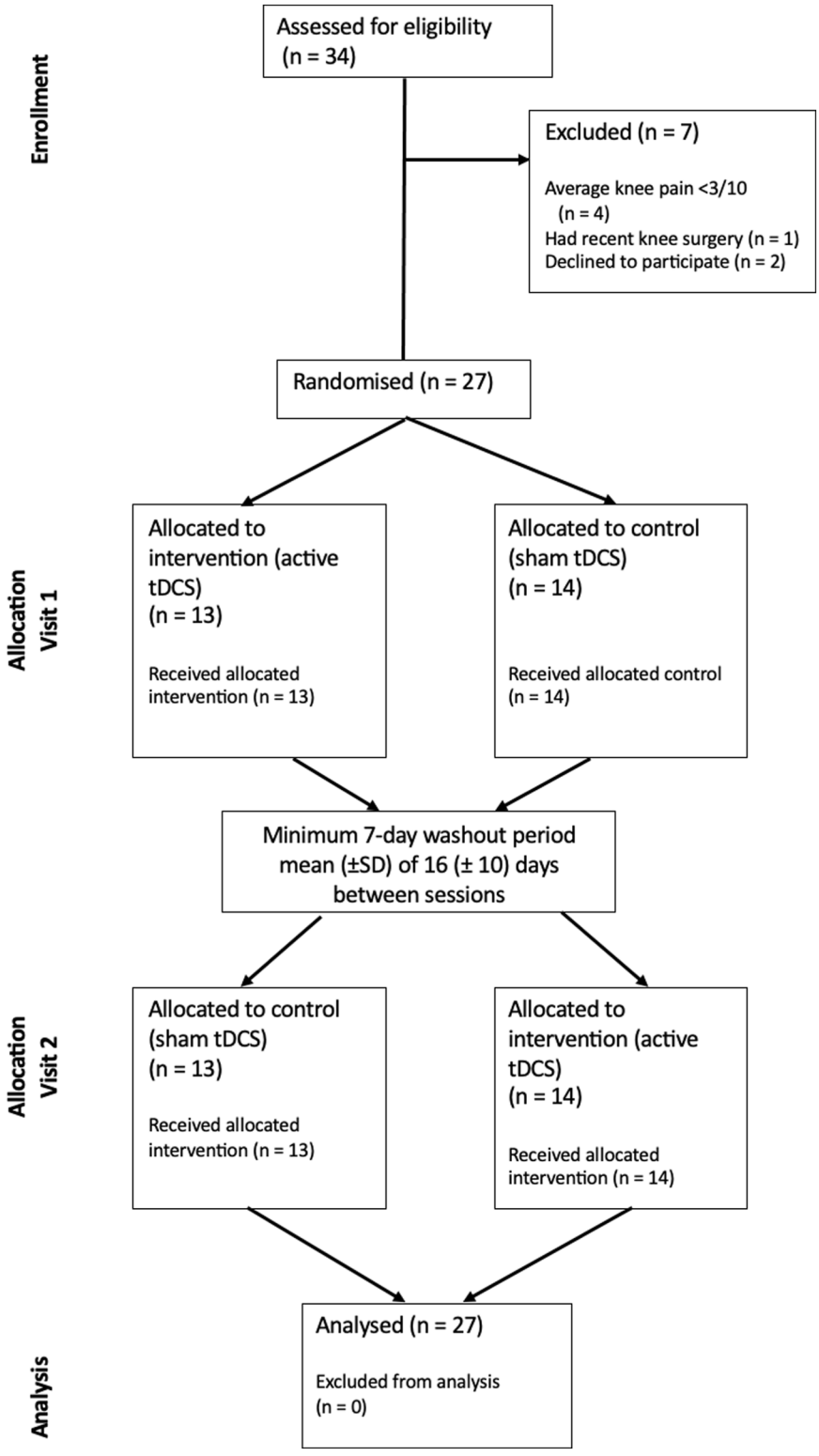

Figure 2. CONSORT flow diagram of the progress through the phases of the randomized cross-over trial for each group.

DISCUSSION

To our knowledge, this is the first study to investigate whether a single session of 2-mA anodal tDCS over M1 enhances EIH compared with sham tDCS in individuals with knee OA. Contrary to our hypothesis, we observed no significant improvement in the EIH response with active tDCS, as assessed by the change in PPT (primary outcome) or change in evoked or resting pain (secondary

Table 1. Baseline Characteristics for Participants Randomized to Receive the Active tDCS or Sham tDCS Session First.

Baseline characteristic	Active tDCS first (n = 13)	Sham tDCS first (n = 14)
Age (y)	61.6 (8.2)	70.6 (9.7)
Sex (female %)	7 (54%)	8 (57%)
Ethnicity: frequency (%)		
New Zealand European	13 (100%)	10 (71%)
Other European	0 (0%)	3 (21%)
New Zealand Māori	0 (0%)	1 (7%)
Height (cm)	174 (11.3)	169 (8.1)
Weight (kg)	92.4 (24.4)	73.6 (13.9)
BMI (kg/m^2)	30.3 (5.6)	25.6 (3.8)
Duration of knee pain (mo)	60 (45-122)	152 (66–255)
LLTQ (0–100)	20.5 (2.9)	21.9 (5.9)
HADS–Depression (0–21)	4.1 (2.7)	4.5 (2.3)
HADS–Anxiety (0–21)	3.9 (2.2)	5.8 (3)
TSK (11–44)	38.8 (7.5)	37.3 (5.5)
PCS (0–52)	5 (4–7.5)	6 (1.75–12.25)
BPI–Ave (0–10)	2.6 (1.5)	2.9 (1.4)
BPI–Worst (0–10)	3 (2.5–6.5)	3 (2–5.75)
BPI–Least (0–10)	0 (0–2.0)	0 (0–1)
BPI–Interference (0–10)	1.6 (1.1–2.6)	2.9 (1.6–3.8)
Peak torque (Nm)	170.9 (77.3)	139.4 (53.4)
EIH testing order (knee first [%])	52	48
Taking any pain medication (%)	2 (15%)	4 (29%)
Types of regular pain medication:		
Paracetamol	1 (8%)	2 (14%)
Antiinflammatories	0 (0%)	2 (14%)
Opioids	1 (8%)	0 (0%)
Anticonvulsants	0 (0%)	0 (0%)
Antidepressants	0 (0%)	0 (0%)

Data are presented as mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables.
BMI, body mass index; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; LLTQ, Lower Limb Task Questionnaire; m, meters; PCS, Pain Catastrophizing Scale; TSK, Tampa Scale for Kinesiophobia.

Table 2. Target Torque, Peak RPE, Time to Failure, Maximum Knee Pain During Contraction on the NPRS, and StEPP Time to Completion Across the Active and Sham tDCS Sessions, for All Participants (N = 27).

Measure	Active tDCS	Sham tDCS
Target torque (Nm)	38.0 (16.2)	38.3 (16.6)
Peak RPE (6–20)	20 (19–20)	20 (19–20)
Time to failure (s)	300 (240–300)	300 (230–300)
Maximum knee pain during contraction NPRS (0–100)	34.8 (30.3)	38.0 (30.4)
StEPP time to completion (preintervention)(s)	64 (57–74)	65 (58–80)
StEPP time to completion (postintervention)(s)	64 (58–72)	65 (57–76)

Data are presented as mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables.

outcomes) between conditions. Participants were effectively blinded, and exercise dose was consistent across sessions, suggesting the null effect was not likely affected by unblinding or differences in exercise intensity. Prior tDCS studies in knee OA have used a range of stimulation parameters and delivery schedules, most commonly using multisession protocols administered in isolation rather than in conjunction with exercise.[13–18]

Our findings align with recent evidence from Lewis et al,[24] who found no additive effect of 2-mA anodal tDCS on EIH during isometric grip exercise in healthy adults. In that study, tDCS neither enhanced nor independently altered pain sensitivity, suggesting that in pain-free populations, exercise alone may induce a maximal hypoalgesic effect that cannot be further augmented. However, the findings differ from Borovskis et al,[23] who observed that in healthy participants experiencing experimentally induced musculoskeletal pain, 20 minutes of 1-mA anodal tDCS of M1 enhanced EIH compared with sham tDCS during an isometric gripping task. The magnitude of EIH observed in the present knee OA cohort appears broadly comparable to that reported in recent studies in healthy adults performing similar isometric exercise tasks, when robust increases in PPTs were observed after exercise alone, with no additional enhancement attributable to anodal tDCS.[23,24] This suggests that endogenous pain modulation was largely preserved in our sample, potentially limiting the capacity to detect additive effects of tDCS.

One potential reason for our null findings may be differences in the nature of pain conditions studied. Experimentally induced pain in healthy participants is typically transient and does not appear to strongly affect pain modulation pathways.[63–65] In contrast, knee OA pain is chronic, involving complex, multifactorial mechanisms such as local and systemic inflammation and persistent neuroplastic changes in nociceptive pathways. It is possible that >one session of tDCS is required to modify EIH in people with knee OA. This is supported by previous intervention studies involving tDCS in people with knee OA, when improvements in clinical pain intensity and measures of endogenous pain inhibition such as CPM have been observed after five to 16 sessions of tDCS.[13–17,19] One study in particular showed superior effects with 15 sessions to those with five or ten sessions.[66] This suggests that although single-session effects of tDCS on EIH may be observed in acute pain models, multiple sessions may be necessary to achieve similar effects in chronic pain conditions such as knee OA. Furthermore, recent evidence suggests that repeated tDCS sessions may be required to induce more durable plastic changes in cortical and subcortical networks involved in endogenous pain modulation, motor output, and clinical pain, which may differ from the short-term mechanistic effects evaluated in the present single-session study.[39]

Considerable interindividual variability in response to tDCS has been consistently reported and is influenced by stable factors (eg, anatomy, genetics), state-dependent factors (eg, baseline excitability), and contextual features of stimulation, including task engagement and stimulation parameters.[67] This individual variability in the response to tDCS, particularly during single session interventions, also may have contributed to our findings.[68,69] Tremblay et al[69] found significant individual differences in corticospinal excitability to a single session of M1 anodal tDCS using different durations (10 and 20 minutes) and intensities (1 mA and 2 mA). The results showed no significant group-level effects and low responder rates, with only 20% to 35% of participants classified as expected responders, highlighting the large interindividual variability in neurophysiologic responses to a single session of tDCS. Furthermore, increasing tDCS stimulation intensity does not lead to a straightforward enhancement of neurophysiologic or

Table 3. Primary and Secondary Outcome Measures Across the Active tDCS and Sham tDCS Sessions.

Measure	Active tDCS	Sham tDCS	Between-session difference [95% CI]	*p*-Value
Knee PPT				
Preexercise (kPa)	211 (96)	242 (112)		
Postexercise (kPa)	274 (121)*	298 (144)*		
Absolute EIH (kPa)	60 (20)	60 (20)	0 [−50, 40]	0.82
Relative EIH (ratio)	1.30 (0.07)	1.29 (0.06)	0.01 [−0.18, 0.20]	
Forearm PPT				
Preexercise (kPa)	267 (86)	299 (106)		
Postexercise (kPa)	312 (98)	318 (105)		
Absolute EIH (kPa)	20 (10)	40 (10)*	−20 [−60, 30]	0.45
Relative EIH (ratio)	1.12 (0.05)	1.18 (0.05)	−0.06 [−0.2, 0.08]	
Resting pain (0–100 NPRS)				
Preintervention	0 (0–0)	0 (0–0)		
Postintervention	10 (0–20)	5 (0–20)		
EIH (resting pain change)	12 (5)*	11 (5)*	1 [−13, 15]	0.89
Evoked pain (0–100 NPRS)				
Preintervention	15 (8.5–27.5)	15 (5–30)		
Postintervention	2 (0–10)	10 (5–27.5)		
EIH (evoked pain change)	−6 (3)*	−7 (3)*	1 [−7, 8]	0.14

Pre- and postintervention values represent observed data and are displayed as mean (SD) or median (interquartile range). Change scores are estimated marginal means (SE) derived from linear mixed-effects models adjusting for baseline values and within-participant correlation. Between-session differences represent the difference in absolute pre–post change scores between active and sham tDCS conditions (active minus sham).
*Indicates significant within-session change from pre- to post intervention ($p < 0.05$).

behavioral outcomes.[68] As such, the individual variability in response to tDCS is likely more pronounced during a single session, when the effects might be more susceptible to transient changes in brain state, such as resting membrane threshold excitability.[70,71] Multiple session interventions might mitigate some of this variability by providing repeated exposure, which could help to homogenize responses across individuals.

Importantly, our population of people with knee OA appeared to have mostly mild-to-moderate symptoms, and many had a hypoalgesic response to exercise, which might have made it difficult to observe additional benefits from active tDCS. For example, it is possible that there was a ceiling effect, whereby participants' endogenous pain modulation systems, including those involved in EIH, were already functioning well, leaving little room for further enhancement by anodal tDCS. This is consistent with previous findings that descending inhibitory pathway function is more impaired in individuals with more severe OA pain.[27,72] In addition, participants were recruited using the NICE clinical criteria for knee OA, which prioritize symptom-based diagnosis and reflect routine clinical practice.[73] Radiographic grading of structural disease severity (eg, Kellgren–Lawrence classification) was not included. The absence of imaging-based grading may limit the generalizability of the present findings to individuals with more advanced structural disease or higher baseline pain severity.

Another important, and related, consideration is the dose of exercise used in our study. There was a median time to failure of 300 seconds and a median peak RPE of 20 in both the active tDCS and sham tDCS sessions, indicating participants sustained high levels of perceived exertion across both conditions. This may have yielded a particularly effective exercise protocol for inducing a robust EIH response,[57] making it difficult to further enhance EIH with tDCS.

A notable strength of this study is the inclusion of secondary measures of EIH that may have more direct clinical relevance to people with knee OA than quantifying EIH using PPT alone. Interestingly, despite observing decreased evoked knee pain and a significant increase in PPT at the knee, indicating reduced pressure pain sensitivity, we observed a modest but statistically significant increase in resting knee pain from pre- to post intervention. This finding aligns with previous research by Christensen et al[74] who reported a decrease in pressure pain sensitivity alongside increased clinical pain intensity after a shoulder abduction exercise program in individuals with chronic neck pain. Such findings illustrate a potential disconnect between pain sensitivity measures and clinical pain intensity in response to exercise. The reasons for this are unclear but may relate to known differences in the neural mechanisms of pain at rest from those of evoked pain in people with OA,[75] or local effects of exercise at the joint (eg, increased nociception) that are subsequently counteracted by systemic effects (eg, increased descending inhibition) after exercise. Because resting pain was measured immediately after exercise, it also is possible this did not capture the full extent of inhibition, which may take time to build up and overwhelm any transient increase in nociception. Future research should explore which measures of EIH (pressure pain sensitivity, resting pain, evoked pain) are better predictors of clinically important outcomes in response to exercise in people with knee OA, such as flares in pain, or the magnitude of pain relief with long-term exercise programs.

From a clinical perspective, our findings suggest that adding a single session of anodal tDCS to a high-intensity isometric exercise stimulus is unlikely to meaningfully enhance acute pain modulation in people with mild-to-moderate knee OA. Future work should focus on identifying patient subgroups with impaired endogenous pain modulation who may be more likely to benefit from adjunctive neuromodulatory approaches.

Despite the strengths of this study, including its robust, randomized, triple-blind cross-over design, there also are some limitations. Notably, an isometric exercise protocol was used to induce EIH, whereas others[27,76] have used aerobic exercise protocols. The isometric protocol aligns with the prevailing methods used to elicit EIH in previous studies involving people with OA.[27,55,76,77] Furthermore,

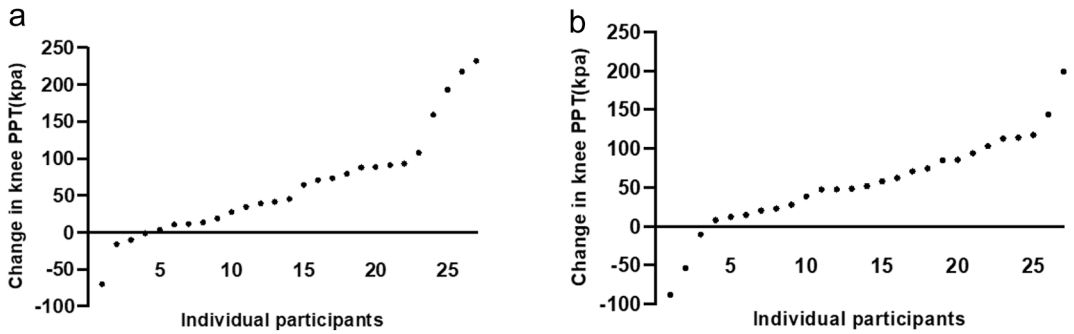

Figure 3. Distribution of the absolute change in knee PPTs from pre- to post intervention for individual participants after M1 anodal tDCS plus isometric exercise (n = 27, left plot) and sham tDCS plus isometric exercise (n = 27, right plot), ordered from the most hyperalgesic (a) to the most hypoalgesic (b) response.

previous studies have shown that aerobic and isometric exercise elicit EIH of a similar magnitude, both in healthy controls[7] and people with knee OA, specifically.[27] For these reasons, it seems unlikely that the type of exercise used to elicit EIH would have substantially affected our results. Notably, the absence of prior research investigating tDCS to enhance EIH in knee OA to inform the calculation of the sample size may have increased the risk of type II error in the present study. Furthermore, the use of one-tailed tests reflects our specific directional hypothesis but limits our ability to detect potential hyperalgesic effects of tDCS and exercise, which, although unexpected on the basis of prior research, cannot be excluded. However, the calculated between-session effect sizes for the primary and secondary outcomes, which ranged from a Cohen's d of −0.19 to 0.05, indicate that a single session of anodal tDCS is unlikely to yield a clinically important effect over sham tDCS, at least in our population.

CONCLUSIONS

A single session of 2-mA anodal tDCS over M1 did not enhance the EIH response to isometric exercise compared with sham tDCS in people with knee OA. It is possible that this reflects a true lack of effect of tDCS in this context. Future studies should consider using multiple tDCS sessions before exercise and/or targeting populations with more severe OA symptoms to further evaluate the potential of tDCS in enhancing EIH. Developing effective methods to enhance EIH may have important clinical implications in people with knee OA, helping to minimize exercise-induced flares in pain and increase both the efficacy of and engagement with exercise-based rehabilitation in the longer term.

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Data Availability

Data are available from the corresponding author on reasonable request.

Authorship Statements

This study was conceived and designed by David Toomey, Gwyn Lewis, Usman Rashid, Natalie Tuck, and David Rice. Data collection was performed by David Toomey. Data analysis and interpretation were conducted by David Toomey, Gwyn Lewis, and David Rice, with input from Usman Rashid. David Toomey prepared the first draft of the manuscript. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the New Zealand Central Health and Disability Ethics Committee (protocol code: 21/STH/128).

Consent for Publication

Participants provided written consent for anonymized data to be used in publications.

Conflict of Interest

The authors reported no conflict of interest.

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REFERENCES

1. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis*. 2014;73:1659–1664.
2. Gibbs AJ, Gray B, Wallis JA, et al. Recommendations for the management of hip and knee osteoarthritis: a systematic review of clinical practice guidelines. *Osteoarthr Cartil*. 2023;31:1280–1292. http://doi.org/10.1016/j.joca.2023.05.015
3. Deloitte AE. The economic cost of arthritis in New Zealand in 2018. https://elsevier.proofcentral.com/en-us/landing-page.html?token=3a7fv823b0135c708869a34493c8f2. Accessed September 5, 2018.
4. Roos EM, Grønne DT, Skou ST, et al. Immediate outcomes following the GLA:D® program in Denmark, Canada and Australia. A longitudinal analysis including 28, 370 patients with symptomatic knee or hip osteoarthritis. *Osteoarthr Cartil*. 2021;29:502–506. http://doi.org/10.1016/j.joca.2020.12.024

5. Lee AC, Harvey WF, Han X, et al. Pain and functional trajectories in symptomatic knee osteoarthritis over up to 12 weeks of exercise exposure. *Osteoarthr Cartil*. 2018;26:501–512. http://doi.org/10.1016/j.joca.2018.01.016
6. Hinman RS, Jones SE, Nelligan RK, et al. Absence of improvement with exercise in some patients with knee osteoarthritis: a qualitative study of responders and nonresponders. *Arthritis Care Res (Hoboken)*. 2023;75:1925–1938. http://doi.org/10.1002/acr.25085
7. Naugle KM, Fillingim RB, Riley 3rd JL. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain*. 2012;13:1139–1150. http://doi.org/10.1016/j.jpain.2012.09.006
8. Rice D, Nijs J, Kosek E, et al. Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. *J Pain*. 2019;20:1249–1266. http://doi.org/10.1016/j.jpain.2019.03.005
9. Andersen LL, Kjaer M, Søgaard K, Hansen L, Kryger AI, Sjøgaard G. Effect of two contrasting types of physical exercise on chronic neck muscle pain. *Arthritis Rheum*. 2008;59:84–91. http://doi.org/10.1002/art.23256
10. White AT, Light AR, Hughen RW, et al. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology*. 2010;47:615–624. http://doi.org/10.1111/j.1469-8986.2010.00978.x
11. Wideman TH, Finan PH, Edwards RR, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. *Pain*. 2014;155:703–711. http://doi.org/10.1016/j.pain.2013.12.028
12. Hansen S, Vaegter HB, Petersen KK. Pretreatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis. *Clin J Pain*. 2020;36:16–24. http://doi.org/10.1097/ajp.0000000000000771
13. Ahn H, Sorkpor S, Miao H, et al. Home-based self-administered transcranial direct current stimulation in older adults with knee osteoarthritis pain: an open-label study. *J Clin Neurosci*. 2019;66:61–65. http://doi.org/10.1016/j.jocn.2019.05.023
14. Ahn H, Suchting R, Woods AJ, et al. Bayesian analysis of the effect of transcranial direct current stimulation on experimental pain sensitivity in older adults with knee osteoarthritis: randomized sham-controlled pilot clinical study. *J Pain Res*. 2018;11:2071–2082. http://doi.org/10.2147/JPR.S173080
15. Ahn H, Woods AJ, Kunik ME, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: an experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimul*. 2017;10:902–909. http://doi.org/10.1016/j.brs.2017.05.007
16. Chang WJ, Bennell KL, Hodges PW, et al. Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: a pilot randomised controlled trial. *PLoS One*. 2017;12:e0180328. http://doi.org/10.1371/journal.pone.0180328
17. da Graca-Tarragó M, Lech M, Angoleri LDM, et al. Intramuscular electrical stimulus potentiates motor cortex modulation effects on pain and descending inhibitory systems in knee osteoarthritis: a randomized, factorial, sham-controlled study. *J Pain Res*. 2019;12:209–221.
18. Suchting R, Colpo GD, Rocha NP, Ahn H. The effect of transcranial direct current stimulation on inflammation in older adults with knee osteoarthritis: a Bayesian residual change analysis. *Biol Res Nurs*. 2020;22:57–63. http://doi.org/10.1177/1099800419869845
19. Martorella G, Mathis K, Miao H, Wang D, Park L, Ahn H. Efficacy of home-based transcranial direct current stimulation on experimental pain sensitivity in older adults with knee osteoarthritis: a randomized, sham-controlled clinical trial. *J Clin Med*. 2022;11:5209. http://doi.org/10.3390/jcm11175209
20. Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. *Front Hum Neurosci*. 2013;7:628.
21. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol*. 2017;595:4141–4150. http://doi.org/10.1113/JP273355
22. Flood A, Waddington G, Cathcart S. High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: a randomized trial. *J Pain*. 2016;17:600–605. http://doi.org/10.1016/j.jpain.2016.01.472
23. Borovskis J, Cavaleri R, Blackstock F, Summers SJ. Transcranial direct current stimulation accelerates the onset of exercise-induced hypoalgesia: a randomized controlled study. *J Pain*. 2021;22:263–274. http://doi.org/10.1016/j.jpain.2020.08.004
24. Lewis A, Rattray B, Toufexis C, Flood A. Does transcranial direct current stimulation enhance the hypoalgesic effect of exercise? *Sportsmed Health Sci*. 2026;8:102–109. http://doi.org/10.1016/j.smhs.2024.12.002
25. Lillywhite A, Woodhams SG, Gonçalves SV, et al. Anxiety enhances pain in a model of osteoarthritis and is associated with altered endogenous opioid function and reduced opioid analgesia. *PAIN Rep*. 2021;6:e956. http://doi.org/10.1097/pr9.0000000000000956
26. Rodríguez-Lagos L, Fernández-Carnero J, Laguarta-Val S, et al. Conditioned pain modulation and temporal summation in patients with knee osteoarthritis: a systematic review and meta-analysis. *J Pain*. 2025;33:105464. http://doi.org/10.1016/j.jpain.2025.105464
27. Fingleton C, Smart KM, Doody CM. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation. *Clin J Pain*. 2017;33:395–404. http://doi.org/10.1097/ajp.0000000000000418
28. Burrows NJ, Booth J, Sturnieks DL, Barry BK. Acute resistance exercise and pressure pain sensitivity in knee osteoarthritis: a randomised crossover trial. *Osteoarthr Cartil*. 2014;22:407–414. http://doi.org/10.1016/j.joca.2013.12.023
29. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. http://doi.org/10.1136/bmj.c869
30. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: extension to randomised crossover trials. *BMJ*. 2019;366:l4378. http://doi.org/10.1136/bmj.l4378
31. Ludbrook J. Should we use one-sided or two-sided P values in tests of significance? *Clin Exp Pharmacol Physiol*. 2013;40:357–361. http://doi.org/10.1111/1440-1681.12086
32. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain Inventory. *Ann Acad Med Singap*. 1994;23:129–138.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–370. http://doi.org/10.1111/j.1600-0447.1983.tb09716.x
34. McNair PJ, Prapavessis H, Collier J, Bassett S, Bryant A, Larmer P. The lower-limb tasks questionnaire: an assessment of validity, reliability, responsiveness, and minimal important differences. *Arch Phys Med Rehabil*. 2007;88:993–1001. http://doi.org/10.1016/j.apmr.2007.05.008
35. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*. 1995;7:524–532.
36. French DJ, France CR, Vigneau F, French JA, Evans RT. Fear of movement/(re) injury in chronic pain: a psychometric assessment of the original. *Pain*. 2007;127:42–51.
37. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. 2001;57:1899–1901. http://doi.org/10.1212/wnl.57.10.1899
38. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist*. 2011;17:37–53. http://doi.org/10.1177/1073858410386614
39. Tapsell LC, Pinto MD, Vallence AM, et al. What are the optimal transcranial direct current stimulation parameters and design elements to modulate corticospinal excitability? A systematic review and longitudinal meta-analysis. *Neurol Res Pract*. 2025;7:86. http://doi.org/10.1186/s42466-025-00449-1
40. Guleyupoglu B, Febles N, Minhas P, Hahn C, Bikson M. Reduced discomfort during high-definition transcutaneous stimulation using 6% benzocaine. *Front Neuroeng*. 2014;7:28. http://doi.org/10.3389/fneng.2014.00028
41. Jeffery DT, Norton JA, Roy FD, Gorassini MA. Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. *Exp Brain Res*. 2007;182:281–287. http://doi.org/10.1007/s00221-007-1093-y
42. Ammann C, Lindquist MA, Celnik PA. Response variability of different anodal transcranial direct current stimulation intensities across multiple sessions. *Brain Stimul*. 2017;10:757–763. http://doi.org/10.1016/j.brs.2017.04.003
43. Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. *Brain Stimul*. 2015;8:1130–1137. http://doi.org/10.1016/j.brs.2015.07.031
44. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;52:3–6.
45. Lewis GN, Rice DA, Kluger M, McNair PJ. Transcranial direct current stimulation for upper limb neuropathic pain: a double-blind randomized controlled trial. *Eur J Pain*. 2018;22:1312–1320.
46. Hanley CJ, Alderman SL, Clemence E. Optimising cognitive enhancement: systematic assessment of the effects of tDCS duration in older adults. *Brain Sci*. 2020;10:304. http://doi.org/10.3390/brainsci10050304
47. Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol*. 2016;127:1031–1048. http://doi.org/10.1016/j.clinph.2015.11.012
48. Newstead S, Young H, Benton D, et al. Acute and repetitive fronto-cerebellar tDCS stimulation improves mood in non-depressed participants. *Exp Brain Res*. 2018;236:83–97. http://doi.org/10.1007/s00221-017-5109-y
49. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25:143–156. http://doi.org/10.1016/j.cct.2003.10.016
50. Kolahi J, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol*. 2009;37:477–484. http://doi.org/10.1111/j.1600-0528.2009.00494.x
51. Williams N. The Borg rating of perceived exertion (RPE) scale. *Occup Med*. 2017;67:404–405.
52. Gomolka S, Vaegter HB, Nijs J, et al. Assessing endogenous pain inhibition: test-retest reliability of exercise-induced hypoalgesia in local and remote body parts after aerobic cycling. *Pain Med*. 2019;20:2272–2282. http://doi.org/10.1093/pm/pnz131
53. Vaegter HB, Lyng KD, Yttereng FW, Christensen MH, Sørensen MB, Graven-Nielsen T. Exercise-induced hypoalgesia after isometric wall squat exercise: a test-retest reliabilty study. *Pain Med*. 2019;20:129–137. http://doi.org/10.1093/pm/pny087
54. Vaegter HB, Dørge DB, Schmidt KS, Jensen AH, Graven-Nielsen T. Test-retest reliabilty of exercise-induced hypoalgesia after aerobic exercise. *Pain Med*. 2018;19:2212–2222. http://doi.org/10.1093/pm/pny009
55. Kosek E, Roos EM, Ageberg E, Nilsdotter A. Increased pain sensitivity but normal function of exercise induced analgesia in hip and knee osteoarthritis–treatment effects of neuromuscular exercise and total joint replacement. *Osteoarthr Cartil*. 2013;21:1299–1307. http://doi.org/10.1016/j.joca.2013.06.019

56. Treister R, Eaton TA, Trudeau JJ, Elder H, Katz NP. Development and preliminary validation of the focused analgesia selection test to identify accurate pain reporters. *J Pain Res*. 2017;10:319–326.
57. Hoeger Bement MK, Dicapo J, Rasiarmos R, Hunter SK. Dose response of isometric contractions on pain perception in healthy adults. *Med Sci Sports Exerc*. 2008;40:1880–1889. http://doi.org/10.1249/MSS.0b013e31817eeecc
58. Farrar JT, Young JPJ, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158. http://doi.org/10.1016/s0304-3959(01)00349-9
59. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Academic Press; 2013.
60. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67:1–48. http://doi.org/10.18637/jss.v067.i01
61. J T, L B, T H, J R, M W, M H. Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin Trials Commun*. 2018;10:80–85. http://doi.org/10.1016/j.conctc.2018.03.008
62. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. Springer; 2009.
63. Oono Y, Wang K, Svensson P, Arendt-Nielsen L. Conditioned pain modulation evoked by a mechanical craniofacial stimulus is not influenced by noxious stimulation of the temporomandibular joint. *J Orofac Pain*. 2012;26:105–116.
64. Szikszay TM, Adamczyk WM, Wojtyna E, Luedtke K. Pain inhibition is not affected by exercise-induced pain. *PAIN Rep*. 2020;5:e817. http://doi.org/10.1097/pr9.0000000000000817
65. McPhee M, Graven-Nielsen T. Alterations in temporal summation of pain and conditioned pain modulation across an episode of experimental exercise-induced low back pain. *J Pain*. 2019;20:264–276. http://doi.org/10.1016/j.jpain.2018.08.010
66. Tavares DRB, Okazaki JEF, Santana MVA, et al. Motor cortex transcranial direct current stimulation effects on knee osteoarthritis pain in elderly subjects with dysfunctional descending pain inhibitory system: a randomized controlled trial. *Brain Stimul*. 2021;14:477–487.
67. Vergallito A, Feroldi S, Pisoni A, Romero Lauro LJ. Inter-individual variability in tDCS effects: a narrative review on the contribution of stable, variable, and contextual factors. *Brain Sci*. 2022;12:522. http://doi.org/10.3390/brainsci12050522
68. Esmaeilpour Z, Marangolo P, Hampstead BM, et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. *Brain Stimul*. 2018;11:310–321. http://doi.org/10.1016/j.brs.2017.12.002
69. Tremblay S, Larochelle-Brunet F, Lafleur LP, El Mouderrib S, Lepage JF, Théoret H. Systematic assessment of duration and intensity of anodal transcranial direct current stimulation on primary motor cortex excitability. *Eur J Neurosci*. 2016;44:2184–2190. http://doi.org/10.1111/ejn.13321
70. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front Cell Neurosci*. 2015;9:181. http://doi.org/10.3389/fncel.2015.00181
71. Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Front Syst Neurosci*. 2014;8:25. http://doi.org/10.3389/fnsys.2014.00025
72. Arendt-Nielsen L, Egsgaard LL, Petersen KK, et al. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. *Eur J Pain*. 2015;19:1406–1417. http://doi.org/10.1002/ejp.651
73. NICE. *Osteoarthritis: The Care and Management of Osteoarthritis in Adults*. National Institute for Health and Care Excellence; 2008.
74. Christensen SW, Hirata RP, Graven-Nielsen T. Altered pain sensitivity and axioscapular muscle activity in neck pain patients compared with healthy controls. *Eur J Pain*. 2017;21:1763–1771. http://doi.org/10.1002/ejp.1088
75. Parks EL, Geha PY, Baliki MN, Katz J, Schnitzer TJ, Apkarian AV. Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. *Eur J Pain*. 2011;15:843.e1–843.14. http://doi.org/10.1016/j.ejpain.2010.12.007
76. Vaegter HB, Handberg G, Emmeluth C, Graven-Nielsen T. Preoperative hypoalgesia after cold pressor test and aerobic exercise is associated with pain relief 6 months after total knee replacement. *Clin J Pain*. 2017;33:475–484. http://doi.org/10.1097/AJP.0000000000000428
77. Bossenger NR, Lewis GN, Rice DA, Shepherd D. The autonomic and nociceptive response to acute exercise is impaired in people with knee osteoarthritis. *Neurobiol Pain*. 2023;13:100118. http://doi.org/10.1016/j.ynpai.2023.100118