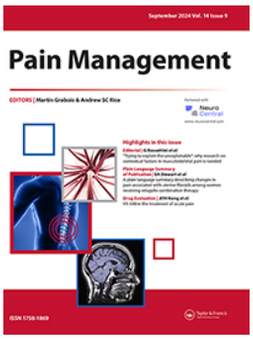

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Comparison of responders and nonresponders with knee osteoarthritis after transcranial direct current stimulation

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PRELIMINARY COMMUNICATION

Comparison of responders and nonresponders with knee osteoarthritis after transcranial direct current stimulation

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ABSTRACT

Aim: The study compared responders and nonresponders to transcranial direct current stimulation (tDCS) regarding clinical pain outcomes in knee osteoarthritis (OA) patients.
Patients and Methods/Materials: Sixty participants received home-based active tDCS, and clinical pain outcomes were compared between responders and nonresponders.
Results: Latent class growth analyses classified 41 participants as responders and 19 as nonresponders. Responders showed significantly greater decreases in pain intensity from baseline to post intervention than nonresponders ($p < .001$). Participants with higher BMI ($p = .02$) and weight ($p = .005$) were more likely to respond, while no significant sociodemographic differences were found.
Conclusions: Identifying characteristics of nonresponsive tDCS subgroups can tailor treatments for each group.
Clinical trial registration: www.clinicaltrials.gov identifier is NCT04016272.

Personalized Brain Stimulation May Improve Pain Relief in Knee Arthritis - Plain Language Summary

There is growing interest in using brain stimulation to help manage chronic pain. One approach, called transcranial direct current stimulation (tDCS), involves applying a gentle electrical current to the brain to alter pain signals. Research shows that tDCS can help reduce pain and improve movement in people with knee osteoarthritis, a common joint condition causing pain and stiffness. However, not everyone experiences the same level of pain relief with this treatment. This study looked at whether certain patient characteristics, like body weight, might influence how well tDCS works. Results showed that tDCS was more effective for people with knee osteoarthritis who have a higher body weight or body mass index (BMI). These findings suggest that tailoring tDCS treatments based on individual characteristics could make pain relief more effective for each patient. By identifying which patients respond best to tDCS, doctors may be able to develop more personalized and effective pain management therapies in the future.

ARTICLE HISTORY
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KEYWORDS
Knee osteoarthritis; transcranial direct current stimulation; older adults; responders to tDCS; BMI

1. Introduction

Knee osteoarthritis (OA) is one of the most prevalent musculoskeletal conditions, characterized by knee pain and restricted activities of daily living and contributing to long-term disability in older adults [1,2]. The disease affects not only the cartilage but the entire joint, including bones, ligaments, the joint capsule, synovium, and surrounding muscles [3]. Since limited physical function and relevant symptoms are strong predictors of disability and dependence, timely management of functional limitations caused by chronic knee pain is crucial for improving outcomes in older adults [1–4].

To manage knee OA pain, treatment includes a range of modalities, from pharmacological interventions, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, to surgical procedures, including joint replacement surgery [4–8]. These approaches are in line with established clinical practice guidelines, such as those from the American College of Rheumatology and the Osteoarthritis Research Society International, which recommend a combination of pharmacological treatments, physical therapy, and, when necessary, surgical intervention to manage symptoms and improve function [9,10]. However, in older adults, pharmacological treatments that include the use of analgesic medications can result in significant adverse effects, such as respiratory depression, confusion, and sedation [11]. Furthermore, the effectiveness of these medications in managing chronic pain in this population is often inconsistent and may not provide the desired relief. Therefore, safe, evidence-based noninvasive and innovative nonpharmacological interventions targeting pain-related brain function are urgently needed [12].

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Article highlights

- While tDCS has gained attention for treating chronic knee pain due to its neuromodulatory effects, this study found no significant differences in sociodemographic variables such as race, gender, education, or OA duration between responders and nonresponders. However, differences in BMI and weight suggest these may influence responsiveness to tDCS.
- The findings indicate that tDCS is effective in reducing clinical pain for patients with knee OA with higher BMI and weight. Further research is needed to assess the underlying biological or psychosocial mechanisms contributing to the benefits of tDCS in this population.
- The findings suggest that identifying responder and nonresponder groups, along with their treatment outcomes, could help to tailor tDCS interventions for this population and reduce the nonresponse rate.

Knee OA pain is associated with increased pain-related brain activity, which may help to explain the limited effectiveness of treatments focused solely on the knee [12–14]. This increased brain activity underscores the need for therapies that address both peripheral knee pain and the central mechanisms involved in pain perception and processing [12,15]. Most conventional therapies, including anti-inflammatory medications, injections, physical therapy, and joint injections, primarily target the nerves at the site of the knee, addressing the pain locally without affecting how the brain processes pain [7,8,16]. However, there is increasing interest in interventions that also target central pain processing mechanisms [17]. One such therapy, transcranial direct current stimulation (tDCS), has gained considerable attention for its neuromodulatory effects in managing chronic pain [18–20].

tDCS is a noninvasive and painless technique that applies low-intensity direct electrical current to the scalp, modulating the resting membrane potentials of neurons and altering the excitability of the targeted cortical area [16,17]. It is known to affect membrane potential, ion channels, synaptic plasticity, and cortical excitability [21]. In addition, tDCS can modulate excitability in both brain hemispheres and influence local cortical and brain network connections [22]. Zhu et al. [23] suggested that noninvasive brain stimulation in OA may engage deeper neuromodulatory processes beyond cortical excitability, expanding understanding of tDCS mechanisms.

While several systematic reviews, meta-analyses [24–28], and previous studies [19,20,29] have demonstrated that tDCS significantly reduces pain intensity and improves functional ability in patients with knee OA, variability in treatment response remains a challenge. Categorizing patients into responder and nonresponder groups may help to reduce this variability and optimize outcomes with tDCS [26,30]. Identifying and categorizing differential responders could advance brain stimulation development and lead to more personalized pain management therapies.

2. Purpose of the study

The responder-nonresponder approach could increase understanding of the tDCS efficacy and help to identify participants who are more likely to benefit from the treatment [24]. Despite variability in response to tDCS in knee OA patients, little is known about the factors that contribute to differential responses. In clinical settings, patients are often classified into responder and nonresponder groups based on their response to tDCS, with different pain mechanisms potentially explaining variations in treatment outcomes.

The objectives of this study were to (a) compare responder and nonresponder groups based on clinical pain outcomes, and (b) identify demographic and clinical factors (e.g., body mass index [BMI]) that distinguish responders from nonresponders. In this study, we classified knee OA patients who received tDCS into two subgroups, responders and nonresponders, using seven classification methods. The classification was based on changes in three pain measures: the Numeric Rating Scale (NRS), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Pain Catastrophizing Scale (PCS). Our analysis compared clinical pain differences between the two groups and identified significant factors that may influence this classification.

3. Methods

The study protocol was registered at www.clinicaltrials.gov (NCT04016272). The study protocol and procedures received approval from the University of Texas Health Science Center at Houston Institutional Review Board (IRB), with approval number HSC-SN-19-0469.

3.1. Design and randomization

A secondary analysis was conducted using data from a double-blind, randomized, sham-controlled, phase II parallel-group study. Participants for the current study were drawn from the active tDCS intervention group in the original randomized clinical trial. In the original study [29], 120 individuals with knee OA were randomized to either the active tDCS or sham tDCS intervention. According to the study protocol, this sample size allowed for detection of an anticipated effect size of 0.89 with more than 99% power at a .05 significance level, accounting for a 10% attrition rate. The smallest detectable effect size was .54, providing 80% power at the same significance level, with attrition considered. Therefore, this sample size was sufficient to detect a clinically meaningful effect.

3.2. Participants

Applicants in the original study were eligible if they (a) were 50–85 years old, (b) had symptomatic knee OA based on American College of Rheumatology Clinical criteria [31], (c) had knee OA pain in the past 3 months with an average of at least 30 on a 0–100 NRS score for pain, (d) were able to speak and read English, and (e) had no plan to change pain medication regimens throughout the trial. Applicants were excluded if they had (a) prosthetic knee replacement or non-arthroscopic surgery to the affected knee; (b) a history of brain surgery, brain tumor, seizure, stroke, or intracranial metal implantation; (c) systemic rheumatic disorders, including rheumatoid arthritis; (d) alcohol/substance abuse; (e) current use of

sodium channel blockers, calcium channel blockers, and NMDS receptor antagonists; (f) diminished cognitive function that would interfere with understanding study procedures (i.e., Mini-Mental Status Exam score ≤ 23) [32]; (g) pregnancy or lactation; or (h) hospitalization within the preceding year for psychiatric illness.

3.3. Study procedures

In the original study (The study protocol was registered at www.clinicaltrials.gov (NCT04016272). The study protocol and procedures received approval from the University of Texas Health Science Center at Houston Institutional Review Board (IRB), with approval number HSC-SN-19-0469), participants self-administered tDCS at home for 15 weekdays (Monday through Friday for 3 consecutive weeks) under real-time supervision by the research staff. tDCS with a constant current intensity of 2 mA was applied for 20 minutes per session daily via the Soterix 1 × 1tDCS mini-CT Stimulator device (Soterix Medical Inc., NY; 6.5 in long, 3 in wide, 0.7 in thick) with headgear and 5 × 7 cm saline-soaked surface sponge electrodes.

During the baseline visit, participants were thoroughly trained on the use of the tDCS device until they were comfortable with the procedure. This training included a demonstration of how to apply the electrodes and operate the device, followed by practice under the supervision of research staff. Participants were then asked to demonstrate application and use of the tDCS device, and feedback was provided until participants could confidently self-administer the treatment. Once the research staff confirmed the participant's understanding of the procedure, the participant was provided with the tDCS device and an organized device kit, prepared by day for ease of use. Also, participants received written instructions in the form of a manual with pictures. The tDCS was applied with the anode electrode placed over the primary motor cortex (M1) and the cathode electrode placed over the supraorbital region (SO). Electrical current was gradually ramped up and down over 30 seconds at the beginning and end of the stimulation period. Remote supervision was carried out using real-time communication via headphones and video calls. During each session, participants were guided through the process step by step to ensure correct electrode placement and proper device operation, and any issues were addressed immediately through this remote communication.

Participants were administered a stimulation session only after being provided a single-use unlock code by the research staff, once proper contact quality was achieved. After entering the unlock code, the device screen displayed a countdown timer. The session automatically ended after 20 minutes and study staff instructed the participant to remove the headset, discard the sponges, and safely store all materials for the next session. For sham stimulation, the electrodes were placed in the same positions as active stimulation, but the device delivered a 2 mA current for only 30 seconds. This sham method was reliable and indistinguishable from active treatment. Study data were collected by the staff using equipment and resources at the PI's laboratory at the participating university. Participants visited the laboratory four times, each time for approximately 2 hours.

3.4. Measures of clinical pain

Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [33], clinical pain intensity was measured using three measures: NRS, WOMAC, and PCS. These clinical outcomes were measured at four distinct time points (baseline, Day 5, Day 10, and Day 15 [post-intervention]).

3.4.1. NRS

The NRS is a simple numeric pain screening tool to assess current clinical pain severity by asking participants to rate their average knee pain over the past 24 hours using a scale of 0 (*no pain*) to 100 (*the worst pain imaginable*). The measure is reliable and has been validated for use with older adults [17,34]. Cronbach's alpha in the current study was α = .869.

3.4.2. WOMAC

Clinical pain intensity was measured using WOMAC [35], which has scores ranging from 0 to 96, with higher scores indicating worse OA pain-related symptoms. The WOMAC was administered to measure self-reported pain and functional ability. The tool is a self-administered scale with 24 questions using a Likert-type response scale from 0 (*no, without difficulty, or no symptom*) to 4 (*unable to engage in activities, or extreme symp*toms). The WOMAC showed a Cronbach's alpha of .95 for pain, and .93 and .85 for the long and short forms, respectively [35]. In the current study, the Cronbach's alpha was α = .917.

3.4.3. PCS

Catastrophic thinking related to OA pain was measured using the PCS, a 13-item self-report questionnaire [36,37]. Participants are asked to assess the degree to which they experience certain thoughts or feelings during pain, using a 5-point Likert-type response scale from 0 (*never*) to 4 (*always*). Total scores range from 0 to 52, with higher scores indicating greater pain catastrophizing. Reliability was good, with values of .87 for rumination, .60 for magnification, and .79 for hopelessness, with the total reliability being .87. In this study, the internal consistency, as measured by Cronbach's alpha, was α = .956.

3.5. Data analyses

3.5.1. Statistical method

R software (R version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) was employed to conduct all statistical data analyses. For the treatment group data, the missing value was checked and removed for subsequent analyses. Summary statistics (e.g., mean, standard deviation) were calculated to describe participants' demographic and clinical characteristics.

Participants were classified into responder and nonresponder groups based on the differences in clinical outcomes between baseline and Day 15 (i.e., post intervention), as well

as on the outcomes at four distinct time points (baseline, Day 5, Day 10, and Day 15). A participant was deemed to be a responder if they reported a ≥ 0-point decrease in pain at Day 15 relative to baseline. Conversely, if the pain report increased from baseline to Day 15, the participant was categorized as a nonresponder.

By calculating the difference in clinical outcomes at various time points (baseline, Day 5, Day 10, and Day 15), seven distinct methods were employed to categorize patients into responder and nonresponder groups: either (a) setting zero, mean, and median as the grouping criteria for the difference in values between baseline and Day 15, or (b) using Latent Class Growth Analyses (LCGA), two Growth Mixture Models (GMM with class-specific random intercepts and GMM with class-specific random intercepts and random slopes) [38] and Group-Based Multivariate Trajectory Modeling (GBMTM) [39] for the differences in values between baseline and the other three time points. Normality assumptions were evaluated by the Shapiro test for the changes in NRS, WOMAC, and PCS scores from baseline to Day 15. Subsequently, those change scores for the responder group and the nonresponder group were compared by Wilcoxon rank-sum test (when the normality assumption was violated) or *t* test (when the normality assumption was not violated).

The generalized linear model was performed together with backward stepwise model selection to identify factors that significantly impacted the classification between the responder group and the nonresponder group. Unless otherwise specified, the significance level for all tests was set to .05.

4. Results

4.1. Sample characteristics

In the original randomized study, a total of 120 eligible participants were randomly and evenly distributed to the sham group ($n = 60$) or the treatment group ($n = 60$). In this study, the 60 participants in the treatment group were included in the analysis. Table 1 shows the demographic and clinical characteristics of all 60 participants. The majority of participants were female (sham group 70.00% [$n = 42$] vs. treatment group 66.70% [$n = 40$]), White (53.3% vs. 43.3%), and holders of 4-year college degrees (31.70% [$n = 19$] vs. 26.70% [$n = 16$]), with an average age of 65.96 years ($SD = 8.41$) and an average BMI of 32.6 ($SD = 8.48$).

4.2. Clinical pain

Seven methods were employed as the grouping basis for the differences among various clinical outcomes (NRS, WOMAC, PCS) and their respective baseline values: (a) using zero, mean, and median as the grouping criteria, or (b) using LCGA, GMM1, GMM2, and GBMTM.

Table 2 and Figure 1 present group classification results for the first four methods. The results from the GMM1, GMM2, and GBMTM approaches were not included for two main reasons. First, all three methods demonstrated inaccuracies in classifying both relatively stable curves and curves with significant trends, especially for GBMTM, which showed no clear trend in classification results (Figure S1). Second, regression analyses based on the classification outcomes of these models did not reveal significant factors in the analysis of potential influencing factors. The relevant classification results for the three methods, including the number of members in each group (Tables S5–S6), summary tables for different outcomes (Tables S7–S12), and comparisons between two groups regarding changes from baseline in clinical pain variables (Table S13), were also presented (Tables S14–S17).

4.3. Zero, mean, and median group criteria

From the results plot (Figure 1), using zero as the classification criterion seemed reasonable but oversimplified. In the treatment group, the mean change scores for NRS, WOMAC, and PCS were −24.07, −10.95, and −4.33, respectively (Table 1), with median scores of −25, −11, and −4, showing a similarity between means and medians. The nonresponder and responder groups were comprised of the same members when assessed using mean and median scores for NRS and WOMAC, with only a slight discrepancy observed in the PCS under the two methods (Table 3).

4.4. Latent class growth analysis

As shown in Figure 1, during implementation of LCGA, three classes were established. Compared with the previous method, the results of LCGA were classified more clearly. Two classes were identified as weak and strong responders, both of which fell within the responder group, represented in Figure 1 by blue and green lines, respectively. For these classes, there was a noticeable downward trend in pain intensity change scores; conversely, the nonresponder group exhibited an upward trend, represented in Figure 1. The percentage of classification results overlapping is presented in Table 3.

Results indicated that more than 65% of the study sample responded to tDCS in clinical pain outcomes: 68.33% in NRS, 73.33% in WOMAC, and 95% in PCS (Table 2). Based on NRS classification, a significant difference in some physical variables was observed between responders ($n = 41$) and nonresponders ($n = 19$): weight ($p = .005$) and BMI ($p = .02$; Table 4). There were no significant differences in age, height, race, education level, marital status, or duration of OA across profiles. According to WOMAC classification, no significant difference was found among those variables (Table 5). PCS-based classification indicated a significant difference between groups only in education level ($p < .001$; Table S1).

Table S2 shows the classification results based on pain intensity changes in NRS, WOMAC, and PCS scores from Day 0 to Day 15; the changes were significantly different between the two groups ($p < .001$). According to grouping results from LCGA, the NRS mean decreases were 34.17 ($SD = 17.40$) from Day 0 to Day 15 for the responder group and 2.26 ($SD = 10.70$) for the nonresponder group; for WOMAC and PCS, the means decreased by 16.43 ($SD = 11.77$) and 5.75 ($SD = 6.64$) for the responder group, respectively; mean scores increased by 4.13 ($SD = 8.05$) and 20.67 ($SD = 12.90$), respectively, for the nonresponder group.

Table 1. Demographic and clinical characteristics of the participants.

Variables	Sham group ($n = 60$)	Treatment group ($n = 60$)	Total ($N = 120$)	p value
Age, M ± SD	66.60 (8.43)	65.32(8.41)	65.96 (8.41)	0.54
Height (in), M ± SD	65.53 (4.33)	66.40 (3.73)	65.97 (4.05)	0.15
Weight (lbs), M ± SD	197.95 (49.53)	205.86 (60.19)	201.90 (55.03)	0.69
BMI, M ± SD	32.52 (8.30)	32.67 (8.73)	32.60 (8.48)	0.90
Gender				0.70
Male	18 (30.00%)	20 (33.30%)	38 (31.70%)	
Female	42 (70.00%)	40 (66.70%)	82 (68.30%)	
Race				0.23
American Indian or Alaska Native	0 (0.00%)	2 (3.30%)	2 (1.70%)	
Asian	2 (3.30%)	6 (10.00%)	8 (6.70%)	
Black African American	22 (36.70%)	19 (31.70%)	41 (34.20%)	
White	32 (53.30%)	26 (43.30%)	58 (48.30%)	
Hispanic or Latino	4 (6.70%)	7 (11.70%)	11 (9.20%)	
Education				0.10
Some school but did not complete high school	1 (1.70%)	1 (1.70%)	2 (1.70%)	
High school degree	18 (30.00%)	12 (20.00%)	30 (25.00%)	
Two-year college degree	10 (16.70%)	12 (20.00%)	22 (18.30%)	
Four-year college degree	19 (31.70%)	16 (26.70%)	35 (29.20%)	
Master's degree	11 (18.30%)	9 (15.00%)	20 (16.70%)	
Doctoral degree	1 (1.70%)	10 (16.70%)	11 (9.20%)	
Maritalstatus				0.698
Married	29 (48.3%)	33 (55.0%)	62 (51.7%)	
Widowed	9 (15.0%)	4 (6.7%)	13 (10.8%)	
Divorced	10 (16.7%)	10 (16.7%)	20 (16.7%)	
Separated	2 (3.3%)	1 (1.7%)	3 (2.5%)	
Never married	7 (11.7%)	7 (11.7%)	14 (11.7%)	
Living with partner	3 (5.0%)	5 (8.3%)	8 (6.7%)	
OA.Time[a], M± SD	69.25 (82.88)	71.35 (75.86)	70.30 (79.12)	0.73
NRS.0[b], **M ± SD**	50.63 (21.77)	55.05 (21.96)	52.84 (21.89)	0.37
NRS.5[c], **M ± SD**	44.77 (24.48)	45.93 (24.94)	45.35 (24.62)	0.82
NRS.10[d], **M ± SD**	43.20 (22.90)	37.98 (22.84)	40.59 (22.93)	0.25
NRS.15[e], M ± SD	49.55 (25.74)	30.98 (22.21)	40.27 (25.69)	<0.001
WOMAC.0[f], M ± SD	43.88 (15.58)	42.00(17.05)	42.94 (16.29)	0.62
WOMAC.5[g], M ± SD	39.03 (17.20)	37.27 (17.12)	38.15 (17.11)	0.61
WOMAC.10[h], M ± SD	36.18 (18.09)	30.42 (16.66)	33.30 (17.56)	0.08
WOMAC.15[i], M ± SD	35.80 (17.55)	31.05 (21.08)	33.43 (19.46)	0.11
PCS.0[j], M ± SD	14.62 (12.08)	15.65 (13.99)	15.13 (13.03)	0.89
PCS.5[k], M ± SD	12.40 (12.96)	11.75 (13.58)	12.08 (13.22)	0.53
PCS.10[l], M ± SD	11.75 (12.21)	9.85 (12.38)	10.80 (12.28)	0.25
PCS.15[m], M ± SD	11.15 (12.00)	11.22 (14.45)	11.18 (13.23)	0.45
Difference in NRS[n], M ± SD	−1.08 (16.46)	−24.07 (21.55)	−12.58 (22.31)	<0.001
Difference in WOMAC[o], M ± SD	−8.08 (10.56)	−10.95 (14.20)	−9.52 (12.54)	0.25
Difference in PCS[p], M ± SD	−3.47 (9.11)	−4.43 (9.01)	−3.95 (9.04)	0.35

[a]The length that subjects had osteoarthritis in months, [b]Numerical Rating Scale (NRS) **a**verage pain in the past 24 hours at baseline, [c]NRS average pain in the past 24 hours on Day 5 of tDCS, [d]NRS average pain in the past 24 hours on Day 10 of tDCS, [e]NRS average pain in the past 24 hours on Day 15 of tDCS, [f]Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain at baseline, [g]WOMAC pain on Day 5 of tDCS, [h]WOMAC pain on Day 10 of tDCS, [i]WOMAC pain on Day 15 of tDCS, [j]Total Pain Catastrophizing Scale (PCS) score at baseline, [k]Total PCS on Day 5 of tDCS, [l]Total PCS on Day 10 of tDCS, [m]Total PCS on Day 15 of tDCS, [n]NRS average pain differences between baseline and Day 15 of tDCS, [o]WOMAC Pain difference between baseline and Day 15 of tDCS, [p]Total PCS scores difference between baseline and Day 15 of tDCS.

Table 2. Classification results for numerical rating scale (NRS), Western Ontario and McMaster universities arthritis index (WOMAC), and pain catastrophizing scale (PCS).

Method	Nonresponder	Responder	Percentage[a]
NRS-Zero	6	54	90.00%
NRS-Median	27	33	55.00%
NRS-Mean	27	33	55.00%
NRS-LCGA	19	41	68.33%
WOMAC-Zero	10	50	83.33%
WOMAC-Median	28	32	53.33%
WOMAC-Mean	28	32	53.33%
WOMAC-LCGA	16	44	73.33%
PCS-Zero	8	52	86.67%
PCS-Median	28	32	53.33%
PCS-Mean	33	27	45.00%
PCS-LCGA	3	57	95.00%

[a]This percentage refers to the proportion of the responders in the treatment group.

Generalized linear model analysis, together with backward stepwise model selection, was conducted to identify potential confounding factors on the clinical outcomes change classification. No significant factor was found for the complete models of the three pain intensities (Table S3). However, with stepwise Bayesian information criterion, BMI was significantly associated ($p = .03$) with NRS score changes (Table S4). For WOMAC and PCS score changes, no significant confounders were detected.

5. Discussion

This study examined the differences in clinical pain outcomes between responder and nonresponder groups among persons with knee OA following tDCS intervention. The LCGA method

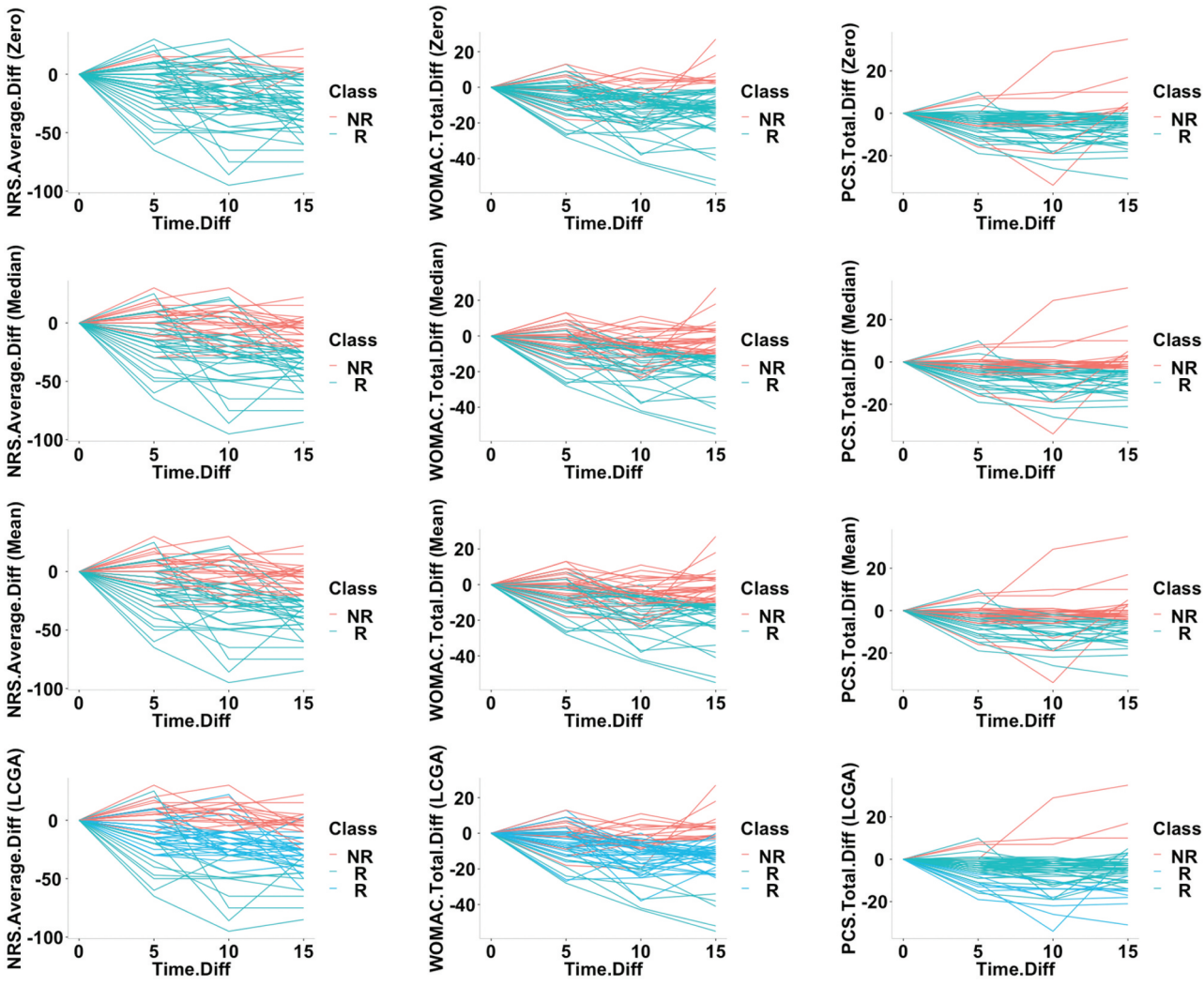

Figure 1. Spaghetti plots for four methods.

Table 3. Percentage of classification results overlapping.

NRS	Percentage	WOMAC	Percentage	PCS	Percentage
Zero-Median	65.00%	Zero-Median	65.00%	Zero-Median	65.00%
Zero-Mean	65.00%	Zero-Mean	65.00%	Zero-Mean	65.00%
Zero-LCGA	75.00%	Zero-LCGA	75.00%	Zero-LCGA	75.00%
Median-Mean	100.00%	Median-Mean	100.00%	Median-Mean	91.67%
Median-LCGA	83.33%	Median-LCGA	80.00%	Median-LCGA	58.33%
LCGA-Mean	83.33%	LCGA-Mean	80.00%	LCGA-Mean	50.00%

identified two distinct groups of participants based on their responses to tDCS treatment. The responder group demonstrated significant improvement in clinical pain intensity (NRS), while the nonresponder group showed a trend toward worsening pain.

We also identified key demographic and clinical factors that differentiated responders from nonresponders. Notably, the responder group had significantly higher weight and BMI compared to the nonresponder group (Weight: 221.06; BMI: 34.51 vs. Weight: 173.05; BMI: 28.69). Previous studies [40–43] have shown that obesity is a strong risk factor for developing knee OA, and elevated BMI has been associated with an increased risk of OA. One explanation could be that individuals with higher BMI experience altered neural plasticity and inflammatory responses, which enhance the effects of tDCS on pain modulation. Also, biomechanical factors such as increased joint loading may make these individuals more responsive to the analgesic effects of tDCS [44,45].

The improvement in pain intensity among responders, compared to the worsening trend in nonresponders, suggests that tDCS may target central pain processing pathways, influencing pain perception or neural sensitization [46]. The variation in group responses could indicate individual differences in neuroplasticity or central sensitization, which may affect tDCS effectiveness [47]. These findings emphasize the importance of central pain mechanisms in understanding variability in tDCS outcomes. This is consistent with previous research [48], which

Table 4. LCGA classification results for NRS.

Variable	Nonresponder ($n = 19$)	Responder ($n = 41$)	Total ($N = 60$)	p value
Age, M ± SD	66.21 (7.90)	64.90 (8.69)	65.32 (8.41)	.73
Height (in), M ± SD	65.00 (3.02)	67.05 (3.88)	66.40 (3.73)	.06
Weight (lbs), M ± SD	173.05 (35.35)	221.06 (63.52)	205.86 (60.19)	.005
BMI, M ± SD	28.69 (4.96)	34.51 (9.51)	32.67 (8.73)	.02
Gender				.17
Male	4 (21.10%)	16 (39.00%)	20 (33.30%)	
Female	15 (78.90%)	25 (61.00%)	40 (66.70%)	
Race				.23
American Indian or Alaska Native	2 (10.50%)	0 (0.00%)	2 (3.30%)	
Asian	2 (10.50%)	4 (9.80%)	6 (10.00%)	
Black African American	5 (26.30%)	14 (34.10%)	19 (31.70%)	
White	9 (47.40%)	17 (41.50%)	26 (43.30%)	
Hispanic or Latino	1 (5.30%)	6 (14.60%)	7 (11.70%)	
Education				.12
Some school but did not complete high school	1 (5.30%)	0 (0.00%)	1 (1.70%)	
High school degree	0 (0.00%)	12 (29.30%)	12 (20.00%)	
Two-year college degree	5 (26.30%)	7 (17.10%)	12 (20.00%)	
Four-year college degree	6 (31.60%)	10 (24.40%)	16 (26.70%)	
Master's degree	3 (15.80%)	6 (14.60%)	9 (15.00%)	
Doctoral degree	4 (21.10%)	6 (14.60%)	10 (16.70%)	
Maritalstatus				.88
Married	10 (52.6%)	23 (56.1%)	33 (55.0%)	
Widowed	2 (10.5%)	2 (4.9%)	4 (6.7%)	
Divorced	4 (21.1%)	6 (14.6%)	10 (16.7%)	
Separated	0 (0.0%)	1 (2.4%)	1 (1.7%)	
Never married	2 (10.5%)	5 (12.2%)	7 (11.7%)	
Living with partner	1 (5.3%)	4 (9.8%)	5 (8.3%)	
OA.Time, M ± SD	51.58(52.83)	80.51 (83.43)	71.35 (75.86)	.20

Table 5. LCGA classification results for WOMAC.

Variable	Nonresponder ($n = 16$)	Responder ($n = 44$)	Total ($N = 60$)	p
Age, M ± SD	66.38 (9.33)	64.93 (8.13)	65.32 (8.41)	.53
Height (in), M ± SD	66.19(3.78)	66.48 (3.75)	66.40 (3.73)	.82
Weight (lbs), M ± SD	213.13 (76.08)	203.21 (54.08)	205.86 (60.19)	.97
BMI, M ± SD	33.90 (10.93)	32.22 (7.88)	32.67 (8.73)	.83
Gender				.68
Male	6 (37.50%)	14 (31.80%)	20 (33.30%)	
Female	10 (62.50%)	30 (68.20%)	40 (66.70%)	
Race				.70
American Indian or Alaska Native	0 (0.00%)	2 (4.50%)	2 (3.30%)	
Asian	1 (6.20%)	5 (11.40%)	6 (10.00%)	
Black African American	7 (43.80%)	12 (27.30%)	19 (31.70%)	
White	6 (37.50%)	20 (45.50%)	26 (43.30%)	
Hispanic or Latino	2 (12.50%)	5 (11.40%)	7 (11.70%)	
Education				.10
Some school but did not complete high school	1 (6.20%)	0 (0.0%)	1 (1.7%)	
High school degree	3 (18.80%)	9 (20.50%)	12 (20.00%)	
Two-year college degree	6 (37.50%)	6 (13.60%)	12 (20.00%)	
Four-year college degree	2 (12.50%)	14 (31.80%)	16 (26.70%)	
Master's degree	3 (18.80%)	6 (13.60%)	9 (15.00%)	
Doctoral degree	1 (6.20%)	9 (20.50%)	10 (16.70%)	
Maritalstatus, M ± SD				.06
Married	8 (50.00%)	25 (56.80%)	33 (55.00%)	
Widowed	2 (12.50%)	2 (4.50%)	4 (6.70%)	
Divorced	0 (0.00%)	10 (22.70%)	10 (16.70%)	
Separated	1 (6.20%)	0 (0.00%)	1 (1.70%)	
Never married	2 (12.50%)	5 (11.40%)	7 (11.70%)	
Living with partner	3 (18.80%)	2 (4.50%)	5 (8.30%)	
OA.Time, M ± SD	53.63 (64.30)	77.80 (79.34)	71.35 (75.86)	.06

demonstrated that active tDCS significantly reduced pain intensity compared to sham tDCS after 15 sessions.

A recent systematic review and meta-analysis [26] on tDCS in patients with knee OA reported statistically significant improvements in chronic pain levels in 12 out of 14 studies, demonstrating superior effects in the active tDCS group compared to the sham group. However, two studies found no significant difference in pain intensity between the groups, which may reflect variability in individual responses.

Jonker et al. [49] and Azizi et al. [50] reported no effect of anodal tDCS (2 mA for 20 minutes) on cortical excitability or participant-specific factors such as BDNF genotype or APLM latency, highlighting variability in response. Similarly, Kold

et al. [51] found that while active high definition (HD) tDCS significantly reduced tonic pain-induced temporal summation, it did not significantly affect nerve growth factor (NGF)-induced pain intensity or pressure pain thresholds. NGF, a key player in pain sensitization, promotes the growth and sensitivity of peripheral nerve endings, contributing to heightened pain perception. These findings suggest that HD tDCS may be more effective in modulating central sensitization rather than directly reducing NGF-induced peripheral pain. This emphasizes the importance of addressing central sensitization mechanisms in future tDCS research to better manage chronic pain in conditions such as OA.

The findings suggest that identifying responder and nonresponder groups could help to tailor tDCS interventions for individuals with knee OA. In this study, weight and BMI were key factors in differentiating responders from nonresponders, with nonresponders typically in the overweight range and responders in the type 1 obesity category. These BMI differences may have influenced treatment outcomes, likely due to the varying effects of excess weight on joint stress and inflammation in OA [40–43]. By identifying these predictors, health care professionals can more effectively distinguish which patients are likely to respond, enabling personalized treatment strategies. This approach could improve adherence and outcomes, optimizing the use of tDCS in clinical practice for OA patients.

The results contribute to existing literature by highlighting the significant variability in response to tDCS among patients with knee OA. Identifying responders and nonresponders underscores the need to understand the impact of tDCS on pain outcomes in a heterogeneous population. Further research is needed to explore reasons for nonresponse, including factors such as medical comorbidities. Future studies could examine whether increasing the duration or frequency of stimulation, adjusting the electrical current intensity, or modifying electrode polarity might enhance tDCS effectiveness [52–54]. Responders might have benefited from additional sessions, as the effects of tDCS are cumulative and typically require multiple sessions to achieve clinically significant results [53]. Further investigation is needed to determine whether some nonresponders could become late responders, achieving meaningful pain improvement after extended treatment [55]. This includes exploring whether additional sessions might lead to significant reductions in pain intensity for those patients.

The efficacy of tDCS therapy varies among individuals with knee OA, likely due to differences in pain mechanisms within the peripheral nervous system and central nervous system (CNS) between responders and nonresponders [56,57]. Customizing tDCS interventions by identifying factors that distinguish responders from nonresponders could enhance treatment outcomes. Pain mechanisms in OA can be assessed using biomechanical markers of inflammation or spinal cord response [49]. Identifying characteristics in subgroups that are unresponsive to tDCS would allow for more tailored interventions. Also, future research should explore peripheral and CNS pain mechanisms in nonresponders to understand their lack of response.

While several studies have explored predictors linked to treatment response in older adults with knee OA [58,59], there remains a paucity of predictors indicating a differential response to specific treatments. The lack of clear guidance creates significant uncertainty on how to optimize treatment selection for the majority of patients.

Although the underlying mechanisms of tDCS warrant further investigation, in line with previous studies [20,26], the findings of the current study suggest that tDCS may be associated with improvements in pain intensity (NRS), physical function (WOMAC), and pain catastrophizing (PCS) in older adults with knee OA, although the mechanisms, including potential effects on central pain inhibition, were not directly explored. This improvement is achieved by mitigating the effects of central sensitization and modulating brain activity in the processing of pain [20]. In another study focusing exclusively on patients with knee OA [60], tDCS exhibited parallel benefits on both experimental pain modulation and clinical pain severity, indicating the presence of a dysfunctional descending pain inhibitory system.

Although the proportion of nonresponders in each pain outcome was relatively small, each subgroup was sizable enough, and their OA pain scores differed significantly from those of the responders, resulting in a discernible impact on the slopes of changes. The findings align with previous research on knee OA, which identified variables such as pain intensity, physical function, and psychological factors as key elements influencing treatment outcomes and decision making in managing OA pain [1,3,9,10,26]. Categorizing responder and nonresponder groups could help to identify unique subgroups of older adults who are more responsive to tDCS, thereby optimizing knee pain treatment. This approach could inform development of future clinical trials and increase the effectiveness of treatment by tailoring tDCS to appropriate populations.

In their systematic review and meta-analysis, Dissanayaka et al. [13] reported that active anodal-tDCS (a-tDCS) could be regarded as both a standalone and adjunct brain stimulation, potentially serving as a nonpharmacological pain treatment in older adults with knee OA. It is reasonable to anticipate that tDCS aimed at improving knee pain would lead to a reduction in pain, as indicated by clinical pain measures.

Nonresponse to tDCS may be attributed to factors such as individual variability or other physiological differences, rather than simply an insufficient dose or intensity. Existing literature, including Lefaucheur et al. [52], suggests 2 mA for 20 minutes as the optimal dose, as higher intensities increase the risk of adverse effects without improving outcomes. The goal in converting nonresponders to responders is to optimize pain management by tailoring treatments to individual clinical profiles. Understanding nonresponse helps clinicians to refine tDCS protocols, improving efficacy and applicability. Identifying differences in pain mechanisms between responders and nonresponders allows for more precise interventions, improving outcomes and reducing the need for invasive treatments [51,53,54]. Further exploration of individual differences is crucial for refining tDCS in knee pain treatment and understanding its effects on responders.

The results of this study highlight significant heterogeneity in the response to tDCS intervention by patients with knee OA, which should be considered a key limitation. Identifying both responders and nonresponders underscores the need for further research to better understand the variability in tDCS outcomes. Future studies should also examine whether adjusting variables such as duration, frequency, or intensity of stimulation, or modifying electrode polarity post-tDCS, could

improve intervention efficacy. Furthermore, research could explore whether patients initially categorized as nonresponders might benefit from additional sessions and whether some might exhibit delayed response over time, potentially yielding meaningful improvements in pain intensity [49].

Self-administered tDCS offers advantages such as increased accessibility, convenience, and the ability to receive treatment at home, which is especially helpful for older adults with mobility challenges [18–20,29]. However, it requires proper training to ensure correct electrode placement, and there may be issues with adherence and technical challenges without clinical supervision [29]. Future studies should evaluate the long-term feasibility and effectiveness of self-administered tDCS compared to clinician-administered treatments.

A limitation of the study is that the need for proper training in electrode placement, as inconsistent adherence or technical issues may arise without clinical supervision, although self-administered tDCS offers advantages such as increased accessibility, convenience, and the ability to receive treatment at home, which is especially helpful for older adults with mobility challenges. Also, most participants were non-Hispanic White, with high education and socioeconomic status, which limits the generalizability of the findings to more diverse populations. These factors, including access to health care and health literacy, may affect response to tDCS, and the results may not apply to populations with lower education or socioeconomic status.

This study focused on socio demographic factors (e.g., race, gender, education, marital status) when profiling responders and nonresponders. We did not include key clinical variables such as pharmacology, prior physiotherapy, physical activity, or comorbidities such as depression, which could significantly influence responses to tDCS. Future research should incorporate these factors to provide comprehensive understanding of treatment outcomes and support personalized care approaches for patients with knee OA. Finally, adherence to the tDCS interventions, specifically regarding the frequency of sessions, was monitored throughout the study. All participants completed the prescribed number of sessions, resulting in 100% adherence to the intervention protocol. This high adherence supports the relevance of identifying responders, as consistent participation is crucial for maximizing the therapeutic potential of tDCS and ensuring optimal treatment use and adherence. This finding underscores the feasibility of the intervention and its potential for successful implementation in future studies.

Despite these limitations, categorization of responders and nonresponders provides important information on the efficacy of tDCS for knee OA. The results also provide direction for subsequent analyses of clinical trials with this nonpharmacological and noninvasive brain stimulation that may lead to determination of clinically meaningful differences in pain outcomes.

While tDCS has been effective in managing knee OA pain, the considerable time and cost associated with traveling to an outpatient clinic for repeated tDCS sessions could pose a significant burden for patients [61], especially for older adults who have limited mobility due to chronic pain and limited access to reliable transportation [62,63]. Thus, self-administered, home-based tDCS may offer a promising solution by increasing patient accessibility and receiving the benefits in managing OA knee pain. The self-administration of tDCS offers several advantages, including increased accessibility, convenience, and the ability to carry out treatments in the comfort of one's home. These factors are particularly beneficial for older adults with mobility issues.

6. Conclusion

The findings suggest that identifying responder and nonresponder groups could help to tailor tDCS interventions and reduce nonresponse rates. BMI emerged as a key factor, with higher BMI in nonresponders linked to less pain relief, indicating its potential role in modulating tDCS efficacy for knee OA pain. Clinicians may need to consider BMI when developing tDCS treatment plans.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethical declaration

This study was conducted with the approval of the University of Texas Health Science Center at Houston Institutional Review Board, with approval number HSC-SN-19-0469, and registered with ClinicalTrials.gov (NCT04016272).

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Author contributions

All authors made significant contributions to the conception of the work, reviewed the article for accuracy, and provided constructive feedback. They approved the final version of the article and agreed to take responsibility for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific contributions are outlined below.

Juyoung Park: conceptualization, methodology, validation, writing, original draft preparation
Heling Tong: methodology, software, formal analysis
Yixin Kang: methodology, software, formal analysis
Hongyu Miao: conceptualization, methodology, software
Lifeng Lin: Writing – review and editing
Rina S. Fox: Writing – review and editing
Ilknur Telkes: Writing – review and editing
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Data availability statement

The data supporting this study's findings are not publicly available due to privacy concerns and the need to protect human subject confidentiality.

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