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STUDY PROTOCOL

Efficacy and Central Mechanism of Shexiang Zhuifeng Analgesic Plaster Combined with Transcranial Direct Current Stimulation in the Treatment of Knee Osteoarthritis: Study Protocol for a Randomized Controlled Trial

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Background: Knee osteoarthritis (KOA) is a chronic pain disorder accompanied by central sensitization, and its treatment remains challenging. While Shexiang Zhuifeng Analgesic Plaster (SZAP) has been shown to effectively alleviate peripheral inflammation and pain, transcranial direct current stimulation (tDCS) can modulate cortical excitability and influence central pain processing. The combination of these two interventions may produce a synergistic "peripheral-central" analgesic effect. This study aims to evaluate the efficacy of this combined approach and utilize neuroimaging techniques to elucidate its underlying central neural mechanisms.

Methods: This randomized, controlled, double-blind study will enroll 48 patients with KOA. They will be equally divided into a treatment group and a control group. The treatment group will receive SZAP combined with tDCS, while the control group will receive SZAP combined with sham tDCS. SZAP will be administered once daily, five days per week, and tDCS will be administered three times per week (alternate days) for four weeks. All outcome measures will be measured at baseline and after four weeks of intervention. Efficacy outcomes include visual analogue scale pain scores and the Western Ontario and McMaster Universities Osteoarthritis Index score. The mechanistic analysis focuses on electroencephalogram power spectral density and functional connectivity analysis.

Discussion: This study will innovatively combine SZAP with tDCS for the treatment of KOA, based on a comprehensive peripheral and central intervention approach. The study will explore the combined efficacy and analyze its potential central mechanisms. This will not only provide valuable clinical treatment approaches for KOA but will also deepen our understanding of the disease's mechanisms.

Trial Registration: ITMCTR (registration number: ITMCTR2025002557), registered on December 27, 2025, https://itmctr.ccebtcm.org.cn/mgt/project/view/2004717515376295936.

Keywords: knee osteoarthritis, traditional Chinese medicine, Shexiang Zhuifeng Analgesic Plaster, transcranial direct current stimulation, central mechanism, electroencephalogram

Introduction

Knee osteoarthritis (KOA) is a chronic degenerative disorder characterized by progressive cartilage loss and clinical manifestations such as pain, joint stiffness, and functionality limited.[1–3] The prevalence of KOA among individuals over

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the age of 40 is estimated at 22.9%, with a continuing upward trend.[4,5] Despite global efforts to develop therapeutic strategies aimed at altering the natural progression of KOA,[6,7] no definitive cure or method exists to reverse its degenerative processes.[8] Patient rehabilitation remains a significant challenge for society. Therefore, finding an effective treatment is of utmost urgency in order to alleviate the burden on society and families.

The current clinical management of KOA predominantly follows a stepwise approach encompassing physical therapy, pharmacological intervention, and surgical procedures.[9] Nevertheless, these conventional treatments predominantly address peripheral pathological mechanisms of the knee joint, concentrating on localized tissue inflammation or structural damage, while neglecting the mechanisms of pain sensitization and central nervous system pathology.[10,11] Notably, the severity of radiographic changes in KOA does not consistently align with clinical symptoms.[12–14] For instance, nearly half of patients with moderate to severe structural damage remain asymptomatic, whereas around 10% experience substantial pain despite normal radiographic findings.[15] This discrepancy suggests that pain in KOA patients cannot be fully accounted for by peripheral pathology alone, underscoring the potential involvement of altered pain processing within the central nervous system.[16] Consequently, increasing evidence emphasizes the need to incorporate central mechanisms alongside peripheral pathology to develop comprehensive KOA treatment strategies.[17–21]

In the context of peripheral pathology, inflammatory responses play a crucial role in the pathogenesis of KOA.[22,23] Shexiang Zhuifeng Analgesic Plaster (SZAP), a traditional Chinese medicine, comprises various herbs and active compounds such as Aconitum, Aconitum root, and Myrrh. These ingredients have been utilized for millennia to alleviate chronic musculoskeletal inflammation and pain. It has also been shown in contemporary studies to effectively relieve rheumatic, joint, and muscle pain.[24,25] Some researchers have investigated its application in KOA, observing some degree of efficacy. However, its precise mechanism of action remains unclear, and the efficacy appears to vary.[26]

At the central level, structural and functional alterations in motor and sensory brain regions are recognized as key mechanisms underlying KOA.[27] Research has demonstrated that activation sites within the motor cortex of individuals with KOA experience significant changes during isometric exercise.[28] In previous work, our research team employed functional near-infrared spectroscopy (fNIRS) to monitor activation in sensorimotor-related brain regions during isokinetic knee exercises in patients with KOA, revealing reduced activation in these regions. Correlation analysis further indicated a negative relationship between activation levels in the contralateral primary motor area (M1) and both pain and functional performance.[29] Transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory technique, modulates cortical excitability and neural network function through the application of a weak, constant current to the scalp.[30,31] Although tDCS has demonstrated a significant analgesic effect in KOA patients, the precise mechanisms underlying this effect remain to be elucidated.

In conclusion, this study proposes an integrated intervention program that combines SZAP and tDCS and evaluates its efficacy in patients with KOA through a four-week intervention trial. Additionally, the research investigates the potential central mechanisms contributing to this efficacy. The findings are anticipated to offer a novel therapeutic perspective for KOA rehabilitation and establish a theoretical foundation for the development of future clinical intervention programs.

Materials and Methods

Study Design

The investigation will be conducted as a double-blind, randomized, controlled trial employing a parallel-group design. The clinical trial protocol is developed in full compliance with the SPIRIT 2025 guidelines (Standard Protocol Items: Recommendations for Interventional Trials) (SPIRIT document).

A total of 48 participants will be recruited and evenly allocated into two groups: Group A, receiving SZAP in conjunction with tDCS, and Group B, receiving SZAP alongside sham tDCS. A simplified flow chart of the study is shown in Figure 1, and the timeline of activities is detailed in Table 1. The clinical trial protocol will be conducted in accordance with the guidelines set forth in the World Medical Association Declaration of Helsinki. It received approval from the Ethics Committee of Shanghai Seventh People's Hospital and has been successfully registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR) under the identifier ITMCTR2025002557.

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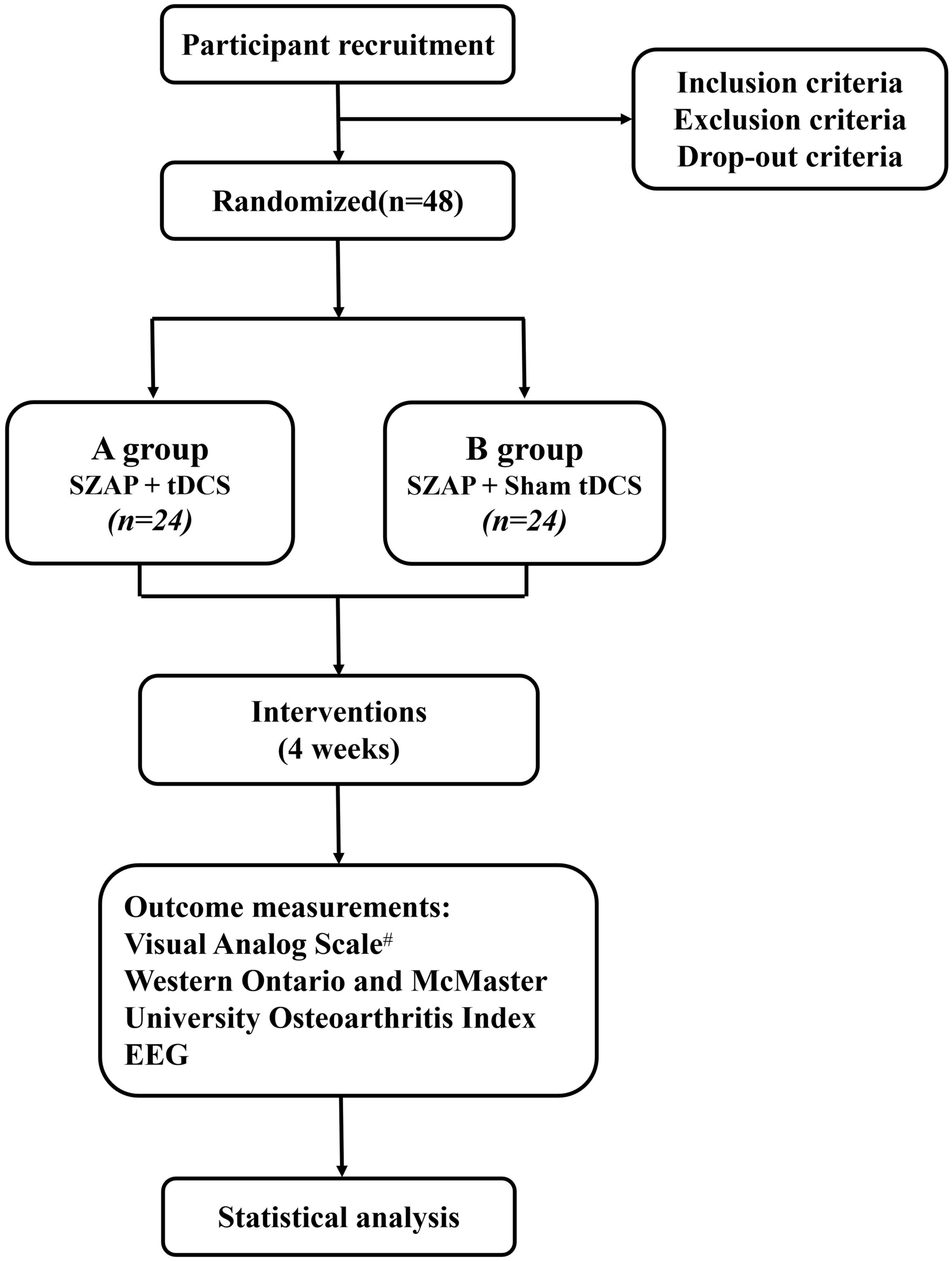

Figure 1 A brief flow chart of the entire study. #: Primary outcomes.
Abbreviations: SZAP, Shexiang Zhuifeng Analgesic Plaster; tDCS, transcranial direct current stimulation; EEG, electroencephalogram.

Sample Size Calculation

The required sample size was calculated through a two-factor repeated-measures analysis of variance (ANOVA), performed with G*Power software (v3.1.9.2, University of Düsseldorf, Germany). Based on previous studies,[18] with an expected effect size (η^2) of 0.06, an α of 0.05, and a power (1-β) of 0.90, and accounting for a 10% dropout rate, we calculated that a total sample size of at least 48 patients was required to achieve adequate statistical power.

Table 1 Schedule of Enrolment, Intervention and Assessments

	Enrollment	Allocation	Post-Allocation			
TIMEPOINT	−1th week	0	1th week	2th week	3th week	4th week
ENROLLMENT:						
Eligibility screen	√					
Informed consent	√					
Demographic information						
Randomization and Allocation		√				
INTERVENTIONS:						
SZAP+ tDCS			√	√	√	√
SZAP+ sham tDCS			√	√	√	√
ASSESSMENTS (Effectiveness):						
VAS		√				√
WOMAC		√				√
ASSESSMENTS (Mechanism of action):						
EEG		√				√

Note: "√": things will be done.
Abbreviations: SZAP, Shexiang Zhuifeng Analgesic Plaster; tDCS, Transcranial direct current stimulation; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; EEG, Electroencephalogram.

Participants

Inclusion Criteria

(1) Meet the diagnostic criteria for KOA established by the American College of Rheumatology (ACR);[32] (2) Age 50–75 years; (3) Disease duration for more than 3 months; (4) The affected area is only the knee joint on one side or the more severe side of both sides; (5) Sign the informed consent form.

Exclusion Criteria

(1) Those who have received other treatments for knee joint problems in the past 3 months; (2) Pregnant or breastfeeding women; (3) Those with neurological diseases (including neurodegenerative diseases, epilepsy, and head injuries); (4) Those with tumors, tuberculosis, rheumatism or rheumatoid arthritis, gout, joint trauma, or any other chronic pain symptoms; (5) Those with a history of mental illness; (6) Those with a history of cardiovascular diseases such as pacemakers and heart stents.

Withdrawal Criteria

(1) The subject withdraws from the study for any reason; (2) The subject's compliance is poor and he or she is unable to complete the assessment and treatment according to the established plan; (3) The subject experiences a serious adverse event; (4) The subject's condition worsens after treatment.

Recruitment, Randomization, and Allocation Concealment

Participants will be recruited from the Rehabilitation Department of Shanghai Seventh People's Hospital and the surrounding community through the distribution of brochures and posters. Eligible potential participants will be informed of all study details and procedures and will voluntarily sign an informed consent form.

Randomization is conducted confidentially by an assistant not directly involved in the study using the randomization system at randomizer.org.[33] A random allocation list will be created, and participants will be numbered sequentially from 1 to 48. Participants will then be randomly assigned in equal proportions to group A or group B.

This assistant will conceal the allocation sequence using sequentially numbered, sealed, opaque envelopes to ensure confidentiality and objectivity, thereby minimizing bias in the selection of participants into the assigned groups.

Blinding

This study is double-blind, and participants and outcome assessors are unaware of their group assignments. Given the specific nature of the intervention, interventional personnel are not subject to blinding. To maximize the success rate of blinding, participants and outcome assessors are blinded after the trial, including inquiries about group assignment and the stimulation status during tDCS intervention.[34] This approach is implemented to control for implementation and measurement bias, thereby maintaining the objectivity and accuracy of the trial results. Furthermore, outcome assessors are not involved in the participant recruitment process to ensure their impartiality.

Interventions

Group A will receive SZAP combined with tDCS stimulation, and group B will receive SZAP combined with sham tDCS stimulation. To ensure the quality and consistency of the interventions, a team of qualified rehabilitation professionals will be responsible for delivering the study interventions. The team consists of licensed physical therapists, each with a minimum of five years of clinical experience. Prior to the study, they will receive standardized training on the methodology to ensure strict adherence to the study protocol and standard operating procedures, including emergency response protocols for potential adverse events.

SZAP

The SZAP used in this study will be a commercially available, ready-to-use product manufactured by Chongqing Xi'er'an Pharmaceutical Co., Ltd., China (National Medicine Approval Number Z20027408). SZAP has a fixed prescription and consistent ingredients. All preparation processes, formulation processes and the proportion of each ingredient are completed in strict accordance with the manufacturer's quality control standards and drug production quality management specifications. SZAP, each 7 cm × 10 cm tablet, consists of Musk Wind-Removing and Analgesic Fluid Extract (artificial musk, raw aconite, raw chuanwu, frankincense, myrrh, raw strychnine seeds, cloves, cinnamon bark, schizonepeta, siler, geranium, cyperus rotundus, Centella asiatica, drynaria root, angelica dahurica, kaempferia galanga, and dried ginger), camphor, borneol, methyl salicylate, menthol, rue extract, belladonna fluid extract, rubber, and rosin. It primarily dispels wind and dampness, dispels cold, and relieves pain. It is used for joint and muscle pain caused by cold-dampness stagnation, as well as sprains.

Specific instructions are as follows:[24] 1) For external use, apply one patch to the affected area once daily, 5 days a week. Apply to the most painful area of the knee joint. If the pain location cannot be described, apply to the inner knee joint. 2) Apply for 6 hours ± 30 minutes. 3) The treatment course is 4 weeks.

tDCS

tDCS is administered using a pair of rectangular surface sponge electrodes (5 cm × 7 cm) soaked in 10 cc of saline. The anode electrode is placed over M1 (C3 or C4, according to the 10–20 system for EEG electrode placement) on the contralateral side of the affected knee, and the cathode electrode is placed over the supraorbital (SO) on the ipsilateral side of the affected knee. A 2 mA direct current is applied, with the current ramping up and down within 10 seconds at the beginning and end of the stimulation period, respectively, for 20 minutes. This is performed three times a week (on alternate days) for four consecutive weeks, for a total of 12 sessions.[21,35]

For sham tDCS, the electrodes are placed in the same locations as above, with the anode over M1 and the cathode over the SO. The current is discontinued 30 seconds after the start of stimulation, but the device is worn continuously until the end of the 20-minute treatment. The duration and number of sessions are the same as above.[21]

Outcome Measurements

Participants will be assessed before and after 4 weeks of treatment. Demographic information, including age, sex, height, weight, body mass index (BMI), disease site, disease duration, and previous or current KOA treatment, will be collected from all participants before randomization. The primary outcome measure is the visual analog scale (VAS) score for pain intensity. This is the core efficacy assessment measure in this study, directly evaluating the analgesic effect of the combined intervention. The secondary outcome measures are the Western University and McMaster University Osteoarthritis Index (WOMAC) and electroencephalogram (EEG). Their functions are to assess the overall improvement in knee pain, stiffness, and joint function, and to explore neurophysiological changes related to pain modulation. Additional outcomes measures are safety outcome measures, including the incidence and severity of adverse events, used to assess the safety characteristics of the intervention. All assessment scales are listed in Table 1.

Primary Outcome

VAS

The primary outcome measure is pain improvement after four weeks of treatment, assessed using a VAS scale. Participants are asked to rate their pain intensity on a scale of 0 (no pain) to 10 (extreme pain).[36] To assess the clinical significance of the change in VAS score, the minimal clinically important difference (MCID) is used, which is set at 1.16 based on previous research.[37]

Secondary Outcomes

WOMAC

Improvement in physical function will be assessed using the WOMAC scale, a widely used tool for functional assessment in KOA patients with high reliability.[38] It consists of three subscales: pain, joint stiffness, and function, with a total score of 96 points, with higher scores indicating worse physical function.

EEG

EEG, as a non-invasive neuroimaging technique, has high temporal resolution and directly measures neuronal activity, making it ideal for capturing rapid cortical dynamics. In addition, recent evidence indicates that specific EEG frequency bands, particularly theta and beta oscillations, are significantly correlated with pain intensity in KOA patients and can serve as objective neurophysiological biomarkers of pain.[39]

EEG Acquisition, Resting-state EEG data are collected from KOA patients before and after treatment using a 32-channel EEG signal acquisition system (ZhenTec NT1, Xi'an ZhenTec Intelligent Technology Co., Ltd., China). Electrodes of the EEG cap are placed according to the international 10/20 system, covering the frontal, central, and parietal brain regions. According to the manufacturer's specifications, CPz is designated as the reference electrode. Patients are seated comfortably, avoiding overt body movement or verbal communication to minimize motion artifacts. Data are collected for approximately 5 minutes with eyes closed, ensuring that the patients are awake. Before recording, the sampling rate is set to 1000 Hz, and a 1–100 Hz bandpass filter and a 50 Hz notch filter are used to mitigate powerline interference.[40] Electrode impedance is adjusted to below 20 kΩ using saline-soaked Lingke cotton.[41] EEG data preprocessing, including channel positioning, data filtering, baseline correction, re-referencing, and independent component analysis (ICA), is performed using the EEGLAB toolbox. During preprocessing, a 1–100 Hz bandpass filter and a 49–51 Hz notch filter are applied. Computing ICA can remove artifacts caused by eye movements and muscle activity, thereby improving the signal-to-noise ratio (SNR) of the EEG data.[42] Finally, the entire dataset is visually inspected for quality assurance.

Power Spectral Density (PSD) Analysis, PSD analysis of EEG signals is performed using a modified Welch periodogram method. The PSD for each channel is calculated using the spectropo function embedded in EEGLAB. To assess PSD in data recorded from a single electrode, PSD values are measured across baseline and post-treatment in different frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), slow gamma (30–55 Hz), and fast gamma (55–100 Hz).[43] By monitoring and analyzing the percentage of power occupied by each EEG frequency band, pain levels can be more objectively assessed. The theta and beta bands may be associated with KOA pain,[39] so the analysis prioritized the theta and beta bands.

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Functional Connectivity Analysis, Undirected functional connectivity analysis is performed using the phase lag index (PLI) in the HERMES toolbox (https://homer-fnirs.org/) to measure zero-lag synchronization between channels. The PLI effectively mitigates volume conduction effects by excluding zero-phase-difference interactions. Its value range is [0, 1], with higher values indicating stronger phase synchronization. The PLI is sensitive to changes in phase synchronization while being unaffected by volume conduction.[44] Based on the SPM8 toolbox (https://www.fil.ion.ucl.ac.uk/spm/software/spm8/), 32 regions of interest (ROIs) corresponding to 32 EEG recording channels are rendered on the cortical surface using the BrainNet Viewer toolbox (http://www.nitrc.org/projects/bnv/). To visualize changes in brain network functional connectivity, each EEG electrode is defined as a node, and the strength of connections between nodes is quantified as edges.[45]

Additional Outcome: Safety

The safety of the trial was assessed by recording adverse events experienced by participants during the study. Adverse events are categorized by severity (mild, moderate, or severe). For example, symptoms such as scalp tingling and periarticular skin irritation that gradually resolved after the intervention is discontinued are considered mild; those that persisted for more than 24 hours are considered moderate; and severe pain and seizures are considered severe. All adverse events are recorded on the patient case report form and analyzed for relevance to the study.

Statistical Analysis

For data exhibiting a normal distribution, continuous variables will be reported as the mean ± standard deviation; for data not conforming to a normal distribution, continuous variables will be expressed as the median and interquartile range. Categorical data will be presented as frequency counts. For continuous data that satisfy the assumptions of normal distribution and equal variance, a two-way repeated-measures ANOVA will be applied to evaluate the interaction between group and time. In cases where these assumptions are not met, the Wilcoxon test will be applied. Categorical variables will be analyzed using the chi-square test. Furthermore, the Pearson correlation coefficient will be utilized to evaluate the relationship between pain and brain functional connectivity, with correlation coefficients classified as low ($r < 0.30$), moderate ($0.30 \leq r < 0.60$), and high ($r \geq 0.60$).[46] The threshold for statistical significance is set at a P-value of less than 0.05. Statistical analyses will be conducted utilizing SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

We established a participation group consisting of KOA patients and rehabilitation physicians. The group discussed the plan and details of this study in detail, improved the research methods and doctor-patient communication procedures, and further enhanced the feasibility of the plan.

Discussion

KOA is often considered a localized injury or degenerative disease around the joint, so treatment often focuses on the affected knee joint. Some researchers have found that while treatments focused solely on the periphery of the knee joint can improve disease progression, their effectiveness is limited and prone to plateauing.[18,47] Recent studies have demonstrated that the pathogenesis of KOA is not only linked to peripheral pathological mechanisms but also closely linked to functional alterations in the M1 region of the central nervous system.[29] Activating the M1 region can improve pain and joint function in KOA patients.[18] However, the combined efficacy of approaches targeting these two mechanisms remains to be further validated. Therefore, this study aimed to investigate the efficacy of SZAP (peripheral intervention) combined with tDCS (central control) in individuals with KOA and to elucidate the potential brain mechanisms by analyzing cortical activity and functional connectivity.

This study has several important advantages. First, it is a comprehensive central and peripheral intervention approach, utilizing both SZAP, which has a significant anti-inflammatory effect, and tDCS, a non-invasive neuromodulatory technique. Both approaches are relatively effective, simple to administer, and readily applicable in clinical practice, offering a potential opportunity for the cure of KOA. Secondly, this study employed a double-blind design to ensure the accuracy and objectivity of the trial results. Not only are VAS and WOMAC scores used to assess clinical improvement, but resting-state EEG is also used to analyze central cortical activity and functional connectivity, and correlation analysis

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between pain and functional connectivity is performed. This is crucial for clarifying the central mechanisms underlying pain improvement in individuals with KOA. Thirdly, this trial strictly adhered to the Medical Research Council's framework recommendations and comprehensively evaluated the trial's innovation, feasibility, and safety.[48]

Importantly, the emerging evidence provides a more nuanced understanding of the neural mechanisms potentially underlying our combined intervention. The evidence has identified specific EEG oscillatory activities as objective biomarkers for pain in KOA.[39] Increased frontocentral high-beta power and reduced central theta power are significantly correlated with pain intensity, suggesting that beta oscillations may reflect maladaptive compensatory mechanisms to joint degeneration, while theta activity might represent a protective or adaptive response.[39,49] These findings position EEG as a sensitive tool for monitoring treatment response. Regarding central mechanisms, neuroimaging studies demonstrate that M1 stimulation not only enhances local cortical excitability but also modulates downstream pain-related regions, including the insular and cingulate cortex, thereby engaging descending pain modulatory pathways.[29,50,51] The integration of SZAP and tDCS may engage a synergistic peripheral-central loop that mutually reinforces therapeutic effects. SZAP's local anti-inflammatory action reduces peripheral nociceptive input from the arthritic knee, which may normalize aberrant afferent signals projecting to the sensorimotor cortex, creating a more favorable neural environment for tDCS-induced neuroplasticity. Conversely, tDCS-mediated enhancement of M1 excitability may strengthen descending pain inhibitory pathways, reduce central sensitization, and amplify the analgesic effects of peripheral anti-inflammation.[51] This improved pain control facilitates better voluntary activation of the quadriceps, increases knee stability, and promotes local blood circulation. These factors may enhance anti-inflammatory of SZAP efficacy by improving drug delivery and reducing pro-inflammatory mediators. Based on the established correlations between EEG oscillations and pain intensity, we hypothesize that intervention-induced clinical improvement will be accompanied by normalization of these aberrant EEG patterns, providing a neurophysiological correlate of treatment response.

This study also has limitations, such as the possible suboptimal tDCS dose and duration, which warrant further investigation. Furthermore, the study focused on central mechanisms, without in-depth investigation of peripheral mechanisms. Furthermore, this study is primarily exploratory and lacked long-term follow-up of patients, which warrants further optimization in future studies.

In summary, the results of this study demonstrate the efficacy and safety of combined therapy, thereby providing new treatment options for clinical intervention in patients with KOA and providing theoretical insights into the central pathological mechanisms of KOA.

Generative AI Statement

The authors declare that no generative artificial intelligence was used in this paper.

Ethics Approval, Trial Registration and Informed Consent

This study received ethics approval from the Ethics Committee of Shanghai Seventh People's Hospital (2025-7th-HIRB-149) and was registered with the ITMCTR (ITMCTR2025002557). All patients will be required to sign informed consent before the start.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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