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Authors

Fillingim, Roger
Woods, Adam
Ahn, Hyochol
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Pain Relief for OsteoArthritis through Combined Treatment (PROACT): Protocol for a randomized controlled trial of mindfulness meditation combined with transcranial direct current stimulation in non-Hispanic black and white adults with knee osteoarthritis

Roger B. Fillingim[1,2,*], **Adam J. Woods**[3], **Hyochol Ahn**[4], **Samuel S. Wu**[5], **David T. Redden**[6], **Song Lai**[7], **Hrishikesh Deshpande**[8], **Georg Deutsch**[8], **Kimberly T. Sibille**[9], **Roland Staud**[10], **Fadel Zeidan**[11], **Burel R. Goodin**[12]

[1]Department of Community Dentistry & Behavioral Science, University of Florida, Gainesville, FL, USA

[2]Pain Research & Intervention Center of Excellence, University of Florida, Gainesville, FL, USA

[3]Department of Clinical and Health Psychology and Center for Cognitive Aging and Memory, University of Florida, Gainesville, FL, USA

[4]Department of Nursing Systems, University of Texas Health Science Center at Houston, Houston, TX, USA

[5]Department of Biostatistics, University of Florida, Gainesville, FL, USA

[6]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL USA

[7]Department of Radiation Oncology, University of Florida, Gainesville, FL, USA

[8]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL USA

[9]Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA

[10]Department of Medicine, University of Florida, Gainesville, FL, USA

[11]Department of Anesthesiology and Center for Mindfulness, University of California San Diego

[12]Department of Psychology, University of Alabama at Birmingham, Birmingham, AL USA

Abstract

Knee osteoarthritis (OA) is a leading cause of late life pain and disability, and non-Hispanic black (NHB) adults experience greater OA-related pain and disability than non-Hispanic whites (NHWs). Recent evidence implicates psychosocial stress, cognitive-attentional processes, and altered central pain processing as contributors to greater OA-related pain and disability among

*Corresponding author. rfilling@ufl.edu.

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NHBs. To address these ethnic/race disparities, this clinical trial will test whether a mindfulness intervention (Breathing and Attention Training, BAT) combined with transcranial direct current stimulation (tDCS) will enhance pain modulatory balance and pain-related brain function, reduce clinical pain, and attenuate ethnic differences therein, among NHBs and NHWs with knee OA. Participants will complete assessments of clinical pain, function, psychosocial measures, and quantitative sensory testing (QST), including mechanical temporal summation and conditioned pain modulation. Neuroimaging will be performed to examine pain-related brain structure and function. Then, participants will be randomized to one of four groups created by crossing two BAT conditions (Real vs. Sham) with two tDCS conditions (Real vs. Sham). Participants will then undergo five treatment sessions during which the assigned BAT and tDCS interventions will be delivered concurrently for 20 minutes over one week. After the fifth intervention session, participants will undergo assessments of clinical pain and function, QST and neuroimaging identical to the pretreatment measures, and monthly follow-up assessments of pain will be conducted for three months. This will be the first study to determine whether mindfulness and tDCS treatments will show additive or synergistic effects when combined, and whether treatment effects differ across ethnic/race groups.

Keywords

Osteoarthritis; Pain; transcranial direct current stimulation; mindfulness; brain imaging; pain modulation

1. Introduction

Osteoarthritis (OA) is the leading cause of pain and disability among older adults [56; 63], and the knee is among the most commonly affected joints, with symptomatic knee OA affecting more than 15 million adults in the US, producing chronic pain, mobility limitations and reduced quality of life [23]. While OA affects people across the entire population, individuals from ethnic and racial minority groups are disproportionately impacted by OA-related pain and disability. Multiple investigators, including our own studies [13; 22; 32], have shown that non-Hispanic black (NHB) adults with knee OA experience greater pain and disability than non-Hispanic whites (NHWs) [3; 4; 22; 59]. Indeed, a recent meta-analysis found that among individuals with knee OA, NHB adults report greater pain severity and higher levels of disability than their NHW counterparts [73]. More recently, Booker and colleagues also reported that NHB adults with knee OA reported higher levels of movement evoked pain than NHW adults with knee OA, even after accounting for radiographic severity of OA and baseline levels of self-reported pain [13].

Multiple biopsychosocial processes contribute to the greater burden of OA-related pain among NHB compared to NHW adults with knee OA. Increasing evidence implicates altered central pain processing as an important driver of pain and disability in knee OA [8; 22; 27; 45], and our quantitative sensory testing (QST) results suggest enhanced pain facilitation and impaired pain inhibition (i.e. pain modulatory imbalance) among NHBs relative to NHWs [22; 32]. Consistent with neuroimaging findings implicating altered pain-related brain structure and function in knee OA pain [48; 58], we have observed ethnic/race group

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differences in pain-related brain structure among adults with or at risk for knee OA [68]. Psychosocial factors also represent potentially important contributors to ethnic/race group differences in pain and disability. Specifically, higher levels of pain-promoting cognitive-attentional processes, such as vigilance and pain catastrophizing [21; 39], may contribute to greater pain and disability among NHBs. Moreover, disproportionate exposure to environmental and psychosocial stress (e.g. discrimination, financial stress) may increase the risk for greater pain and disability among NHBs [12; 31]. Indeed, perceived stress was more strongly associated with movement-evoked pain in NHB versus NHW adults with knee OA [13].

Based on these findings we hypothesize that ethnic/race group differences in psychosocial stress and cognitive-attentional processes negatively impact central pain processing, leading to greater OA-related pain and disability among NHBs (Figure 1). Thus, an optimal intervention strategy to address ethnic/race disparities in OA pain would target psychosocial stress and attentional processes, and corresponding brain networks mediating central pain processing. In order to accomplish this, we have designed a proof-of-principle randomized controlled clinical trial to test whether the combination of a mindfulness meditation intervention targeting attention, affect and stress (Breathing and Attention Training, BAT) and a treatment targeting central pain processing (transcranial direct current stimulation, tDCS) will enhance pain modulatory balance and pain-related brain function, reduce clinical pain, and attenuate ethnic differences therein, among NHBs and NHWs with knee OA. Each treatment alone has previously shown pain relieving effects in musculoskeletal pain [1; 15; 55; 74] however, the proposed trial represents the first attempt to determine whether the treatments will show additive or synergistic effects when combined, and whether treatment effects differ across ethnic/race groups.

2. Material and Methods

2.1. Overview of Study Design

This is not an efficacy trial, rather a proof-of-principle mechanistic trial designed to examine the effects of tDCS and BAT, alone and in combination, on psychophysical and neuroimaging markers of central pain processing as well as clinical pain and function. Figure 2 provides a flow diagram for the protocol. Potential participants will be screened via telephone to determine initial eligibility, and qualified candidates will be scheduled for the first in-clinic Health Assessment Session, which includes additional assessments of eligibility as well as assessments of clinical pain and function and psychosocial variables. A QST protocol will assess mechanical pain sensitivity, including mechanical temporal summation and conditioned pain modulation. This will be followed by a Neuroimaging Session to examine pain-related brain structure and function. Participants will then be randomized to one of four treatment conditions created by crossing two BAT groups (Real vs. Sham) with two tDCS groups (Real vs. Sham). All participants will then undergo five treatment sessions over a one week period during which the assigned combination of BAT and tDCS interventions will be delivered concurrently for 20 minutes. Clinical pain will be assessed on each treatment day, and after the fifth intervention session, participants will again undergo functional, QST and neuroimaging assessments identical to the pretreatment

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measures. After completion of the in-clinic visits, monthly follow-up assessments of pain will be conducted online or by phone for three months.

2.2. Specific Aims & Hypotheses

Based on previous evidence, we propose that ethnic/race group differences in psychosocial stress and pain-related cognitive-attentional processes negatively impact pain-related brain structure and function, and adversely affect pain modulatory balance among NHB relative NHW adults; thereby, leading to greater knee OA-related pain and disability among NHBs. Hence, treatments that target these psychosocial and brain mechanisms will reduce knee OA pain and disability. Therefore, we propose to test whether a five-day course of a mindfulness meditation intervention (Breathing and Attention Training, BAT) and tDCS, and their combination, can enhance pain modulatory balance and pain-related brain function, reduce clinical pain, and attenuate ethnic differences therein, among NHB and NHW adults with knee OA.

Aim 1: To determine the independent and combined effects of brief BAT and tDCS interventions (vs. their respective sham conditions) on pain modulatory balance, pain-related brain function, and knee OA-related pain and disability among NHB and NHW adults. We hypothesize that compared to the combination of sham BAT and sham tDCS, active tDCS and active BAT will: 1a) Enhance pain modulatory balance by reducing pain facilitation and increasing pain inhibition; 1b) Normalize resting and pain-evoked cerebral blood flow in pain-related regions of interest (ROIs); and 1c) Reduce clinical pain and disability and improve functional performance. We anticipate that the combination of active tDCS and active BAT will produce the largest effects, showing evidence of additivity or even synergy.

Aim 2: To determine ethnic group differences in the independent and combined effects of brief BAT and tDCS interventions (vs. their respective sham conditions) on pain modulatory balance, pain-related brain function, and OA-related pain and disability among NHB and NHW adults with symptomatic knee OA. We hypothesize that active BAT and active tDCS, independently and in combination, will produce: 2a) Greater improvements in pain modulatory balance among NHBs compared to NHWs; 2b) Greater decreases in resting and pain-evoked cerebral blood flow in pain-related regions of interest among NHBs compared to NHWs; and 2c) Greater improvements in clinical pain, disability, and functional performance among NHBs compared to NHWs. We anticipate that the combined active treatments will produce the largest benefits for NHBs compared to NHWs. We expect greater treatment effects among NHBs, as our previous findings suggest that the risk factors targeted by these treatments produce greater adverse consequences among NHBs with knee OA.

Aim 3: To identify biopsychosocial predictors and mediators of treatment-related improvements in clinical pain and disability following BAT and tDCS among NHBs and NHWs with symptomatic knee OA. We hypothesize that improvements in clinical pain and disability following BAT and tDCS will be mediated by treatment-induced adaptive changes in: 3a) Pain modulatory balance assessed via QST; 3b) Resting state and stimulus-evoked pain-related regional cerebral blood flow; and 3c) Perceived stress, pain catastrophizing, and

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mindfulness. In addition, we will conduct analyses to identify pre-treatment variables that predict treatment response, including pain-related brain structure and function, pain modulatory balance, and psychosocial variables. We will examine separate multivariable models for each ethnic group to identify mediators and predictors of treatment effects that differ for NHBs and NHWs.

2.3. Study Sites & Coordination across Sites

This trial will be conducted at two study sites, the University of Florida (UF) and the University of Alabama at Birmingham (UAB). The trial is registered at ClinicalTrials.gov (NCT03884374). Consistent with NIH policy, the project will use a single IRB at the University of Florida. Each study site will assign a lead Study Coordinator who will be responsible for administration of the protocol in collaboration with the site PI. This will include coordination of staff training and certification, assignment of staff to study activities, and ensuring effective communication both locally and across the entire study team. Both study sites will use identical study methods as described in the protocol and the detailed Manual of Procedures. The study sites will use a centralized REDCap data management system and a common document library hosted via Microsoft Sharepoint. PROACT will adopt multiple strategies to promote open and consistent communication within the study team, including: 1) Biweekly Videoconferences attended by investigators and study staff, 2) Online Discussion Groups to facilitate communication regarding protocol issues or study concerns, and 3) Annual Investigator Meetings for intensive review and discussion of the protocol and for recalibration of study staff, as needed. These communication strategies are designed to enhance consistency between sites and to provide timely responses to questions or concerns that arise over the course of the study.

2.4. Participants

The PROACT Study aims to enroll 360 adults between the ages of 45 and 85 years who meet American College of Rheumatology (ACR) Clinical Criteria for knee OA, half of whom will be NHB and the other half NHW. Each study site will enroll 180 participants over approximately 4 years. Our inclusion and exclusion criteria are designed to facilitate enrollment of a representative sample of NHB and NHW adults with knee OA while optimizing participant safety and validity of study findings.

2.4.1. Inclusion Criteria.—We will enroll participants between 45 and 85 years of age with unilateral or bilateral symptomatic osteoarthritis of the knee based on the 1986 American College of Rheumatology (ACR) criteria [5], which are:

Knee pain, plus at least 3 of the following 6 signs/symptoms:

- Age > 50 years
- Morning stiffness < 30 minutes
- Crepitus
- Bony tenderness
- Bony enlargement

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- No palpable warmth

Individuals with knee OA who also report pain in other sites of the body will be eligible, as long as the knee is the primary site of pain. People of both sexes will be recruited, and it is anticipated that the sample will include approximately 65% female and 35% male, based on the prevalence of symptomatic knee OA [56; 63].

2.4.2. Exclusion Criteria.—Participants will be excluded if they have medical or arthritic conditions that could confound symptomatic knee OA related outcome measures, or coexisting diseases that could preclude successful completion of the protocol. Specifically, the following exclusion criteria will be applied:

- Systemic rheumatic disease/condition (e.g. rheumatoid arthritis, systemic lupus erythematosus)
- A history of clinically significant surgery to the index knee
- Uncontrolled hypertension (≥ 150/95)
- Neurological disease (e.g. Parkinson's, multiple sclerosis)
- Cardiovascular or peripheral arterial disease
- Daily use of opioids
- Use of sodium channel blockers, calcium channel blockers and NMDA receptor antagonists, because these medications can block tDCS effects.
- Serious psychiatric disorder requiring hospitalization within the past 12 months or characterized by active suicidal ideation
- Diminished cognitive function that would interfere with completion of study procedures
- Pregnancy
- Contraindications to MRI scanning

2.5. Recruitment, Screening and Enrollment

Each site will implement a multimodal recruitment plan that includes community-based and clinic-based strategies, tailored to meet site-specific recruitment needs. Recruitment methods will be developed and continually monitored and modified with support from the Clinical UF Clinical Translational Science Award (CTSA) at each study site. Community-based recruitment efforts will include: recruitment flyers, newspaper ads, radio ads, and ads in other electronic and print media. Additional recruitment strategies may include advertisement on social media and direct mailing of recruitment materials. Each site also has the capability for recruitment of participants from the clinical setting. The CTSA at each site has created an electronic data repository, which allows investigators to query electronic health records to facilitate recruitment of participants. In addition, each site has relationships with primary care and Rheumatology clinics that see large numbers of patients with knee OA, and recruitment from these clinics will be implemented as needed. Recruitment efforts

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will be titrated to maintain consistent participant flow and avoid excessive wait times. Recruitment will be monitored continually via the data management system.

Potential participants will complete a scripted telephone screening to determine initial eligibility. These computer assisted telephone interviews will be conducted by trained study staff using REDCap. The interview is divided into three sections: 1) initial explanation of the study and obtaining verbal consent to proceed with the interview; 2) collection of contact information and demographic data; and 3) screening interview to determine eligibility. If eligible, the participant will then be scheduled for the first study visit, at which time verbal and written informed consent will be obtained.

2.6. Randomization and Scheduling

In order to determine eligibility to proceed with randomization, all data from screening and baseline assessment visits must be entered into REDCap and the eligibility criteria must be met. If the participant is eligible, the two pre-treatment study visits will be scheduled. After all pre-treatment assessments are completed and all data are entered, if the participant remains eligible, randomization will occur immediately prior to the first intervention visit. The Data Analysis Core will perform randomization using a block randomization with stratification for study site, sex, and ethnicity/race in double blind fashion. The UF biostatistician (S.W.) will oversee the randomization procedure and will maintain the randomization codes. Specifically, once study eligibility is confirmed following complete entry of data from both baseline visits, REDCap will automatically generate an email to the study biostatistician providing the information necessary for randomization (ID#, Study Site, Race, and Sex) and the interventionist assigned to this participant. Within 24 hours, the Data Analysis Core will send an email to the interventionist assigned to that participant that contains two numeric codes: a unique 4-digit BAT code for BAT-Active versus BAT-Sham assignment, and a unique 6-digit STIM code for tDCS condition (actual vs. sham) that will be entered into the tDCS stimulator. Only that interventionist will receive information regarding which BAT treatment the code represents. The tDCS stimulation code assigned during randomization will be entered into the tDCS stimulator at each visit, which will determine whether the participant receives sham versus active tDCS. Because the codes are pre-programmed into the tDCS unit, both the interventionist and the participant will be blinded to tDCS condition.

2.7. Blinding & Expectation Management

As noted above, all study staff will remain blinded to tDCS condition, and only the BAT interventionist will be unblinded regarding the BAT condition. The interventionist will not be involved in collection of pre- or post-treatment outcome measures. Participants will remain blinded regarding both conditions. The sham tDCS condition involves a brief period of initial stimulation that mimics the initial experience of tDCS and helps to maintain blinding [29]. Also, participants complete a questionnaire assessing tDCS-induced sensations after each session, and these can be compared between active and sham conditions. Regarding BAT, participants are informed that they will be assigned to one of two BAT conditions, BAT-Standard or BAT-Focused, but they are not informed that the former refers to sham and the latter to active BAT. The differences between these two

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conditions are described below in the section on interventions. To assist with expectation management, the following script is delivered to each participant before the intervention commences:

> The goal of PROACT is to study how two different treatments affect arthritis pain. As a study team, we do not know whether these treatments will help your pain or not, and if they do, we don't know which combination of treatments will be most helpful. That is why we are doing the study. So, we would like you to dismiss any expectations you have about the treatments and simply provide us with the most accurate information you can throughout the study.

To determine whether blinding was adequately maintained, participants will be asked following the intervention which treatments they believe were received after study completion.

2.8. Trial Design

The PROACT Study is a randomized mechanistic proof-of-principle trial designed to determine whether tDCS (vs. sham), BAT (vs. sham), and their combination can modulate central pain processing and clinical pain in NHB and NHW adults with knee OA. The intervention period is five sessions. The interventions are delivered simultaneously, with each intervention session lasting approximately twenty minutes. All interventions will be delivered to participants individually. The goal is to schedule intervention sessions on consecutive days, Monday through Friday whenever possible. We recognize that this will not always be possible and that some intervention periods will occur whereby a weekend separates some of the intervention visits. When possible, intervention visits will be scheduled at the same time every day; however, the study team will allow flexibility in scheduling to accommodate participant needs. Outcome measures will be ascertained in two baseline visits and a single post-treatment visit, and potential mediator variables (e.g. perceived stress, catastrophizing) will be assessed across the two baseline visits. Follow-up data will be collected online via REDCap or using a telephone interview each month for three months. A timeline for the protocol is provided in Table 1 below.

3. Interventions

3.1. Breathing and Attention Training (BAT).

We will describe the mindfulness meditation intervention to participants as Breathing and Attention Training (BAT), because: 1) this terminology will be more understandable compared to mindfulness for many of our participants; 2) it avoids many of the highly varied positive and negative biases that participants often have toward mindfulness meditation; and 3) it prevents the need for deception in the standard-BAT group, as they, too, are undergoing a breathing and attention intervention. For both intervention conditions, participants will be instructed not to practice outside of the intervention sessions in order to maintain consistency in exposure to the intervention.

3.1.1. Focused-BAT.—The Focused-BAT intervention is based on a well-validated mindfulness-based mental training regimen to teach participants to independently practice

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mindfulness meditation [79–84]. Participants will undergo five sessions each lasting approximately 20 minutes. This intervention incorporates principles of mindfulness by having the participant practice intentional attention to breathing sensations and emphasizing nonjudgmental awareness of arising sensations, feelings and thoughts. Participants will be asked to close their eyes, focus on the breath sensations, recognize distracting thoughts and feelings, and to "simply let go" of sensory events without judgment. They will be taught that perceived sensory and affective events are "momentary" and "fleeting" and do not require evaluation. Also, individuals will be instructed to focus on the breath occurring at the tip of the nose and "full flow of the breath". They will also be taught to attend to sensory events without judgment. Then, the principles will be reiterated, and participants will be encouraged to practice these skills while listening to an audio recording of MRI sounds, in preparation for the post-treatment neuroimaging session. In the fourth and fifth sessions, participants will receive minimal instructions, and will meditate during an audio recording of the MRI sounds [80; 84]. A brief description of each of the five intervention sessions is provided below.

- Session 1. Introduction to the BAT intervention, breathing instructions, focus on the breath
- Session 2. Continued focus on the breath, breath sensations, full flow of breathing, non-judgmental awareness
- Session 3. Continued practice with fewer verbal instructions, focusing on the breath, non-judgement awareness
- Session 4. Reiteration of principles, practice while listening to MRI sounds
- Session 5. Limited instructions, participant encouraged to practice on their own while listening to MRI sounds

3.1.2. Standard-BAT.—The main purpose of the Standard-BAT intervention is to incorporate most of the general aspects of the Focused-BAT intervention but *without the specific instructions related to mindfully attending to the breath in a non-evaluative manner* [80; 85]. This regimen is designed so that the primary difference between the focused and standard BAT is the Focused-BAT group's explicit mindfulness-based instructions (e.g., mindful attention to the breath). Thus, the Standard-BAT group can truthfully be told that they have been randomly assigned to a BAT intervention, and previous research has shown that both BAT interventions produce decreases in pain sensitivity [80; 85]. In each session, participants will be instructed to close their eyes, and to take a deep breath "as we sit here in meditation" every 2–3 minutes [80; 85]. All other aspects (training room, posture, facilitator, time providing instruction) of the sham-BAT intervention will be matched. The MRI scanner sounds will be introduced during training in sessions four and five, when participants will receive minimal instruction and will "meditate" during an audio recording of the MRI sounds. The topics covered in each Standard-BAT session are listed below.

- Session 1. Introduction to the BAT intervention, breathing instructions
- Session 2. Continued breathing instructions
- Session 3. Continued breathing instructions

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- Session 4. Instructions to practice breathing while listening to MRI sounds
- Session 5. Limited instructions to continue practicing breathing while listening to MRI sounds

3.2. Transcranial Direct Current Stimulation (tDCS).

Previous studies of tDCS for musculoskeletal pain have predominantly directed stimulation to the primary motor cortex (M1), including the recent pilot study demonstrating significant pain reducing effects of tDCS among older adults with knee OA conducted by members of our team [1]. A Soterix 1×1 Clinical Trials Direct Current Stimulator will apply 20 minutes of 2.0mA direct current through two bicarbon rubber electrodes encased in saline-soaked sponges. The anode will be placed over M1 (C3 or C4 according to the 10–20 system) contralateral to the index knee, and the cathode over supraorbital (SO) cortex (Fp1 or Fp2) ipsilateral to the index knee. Participants will receive twenty minutes of stimulation in each of five visits over one week. *Sham tDCS*. Sham stimulation procedures will be identical except for the duration of stimulation. Participants will receive 30 seconds of 2 mA (30s ramp up/down) of stimulation at the beginning of the session, but the intervention period will continue for 20 minutes to maintain blinding of both participant and interventionist. Because participants habituate to the tingling/prickling sensation of active tDCS within 30–60 seconds of stimulation, sham tDCS provides the same sensation of tDCS without the full duration of stimulation, making it a highly effective sham procedure. *Blinding*. The device has built-in RCT double blinding protocols. Soterix will communicate only with the statistician to de-identify data. *Electrode locations* will be identified using the international 10–20 measurement system. *Electrode site preparation* will involve parting the hair at the electrode site, using plastic hair clips when needed, and placing the electrode as close to the scalp as possible. *Electrode preparation* will involve saturating a sponge electrode with exactly 10cc of 0.9% saline solution using a marked syringe (5cc/side) to provide adequate electrode saturation without oversaturation. *Electrode placement* will involve placing electrodes in an adjustable head-size/M1-SO montage-specific Soterix Easystrap. *Impedance quality* will be ≤15kΩ to ensure proper stimulation of brain tissue. These methods follow field consensus standards as described in a recently published manuscript led by Woods [76].

3.3. Interventionist Training

In order to ensure high fidelity of both interventions, we will implement systematic training and certification procedures for both BAT and tDCS interventionists.

3.3.1. BAT Certification.—BAT interventionists will be doctoral students or post-doctoral professionals in psychology or another health-related discipline. The training and certification process will proceed as follows. Each interventionist will study the detailed scripts for both Focused-BAT and Standard-BAT. They will then practice delivering the interventions until comfortable, at which time the interventionist will have their delivery of the intervention reviewed by a PROACT mindfulness expert (FZ or his certified mindfulness facilitator designee) and feedback will be provided. This process will continue until the interventionist is able to deliver the intervention with high fidelity consistent with the script,

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at which time s/he will be certified to provide the BAT intervention for the PROACT Study. Each site will train multiple BAT interventionists to enable flexibility in scheduling and to support consistent recruitment of participants.

3.3.2. tDCS Certification.—tDCS interventionists will be thoroughly trained in electrode preparation and placement based on careful head measurement and in safe operation of the tDCS device. tDCS training will be overseen by our tDCS expert (AJW), who has provided detailed written and video instructions on head measurement, electrode preparation, electrode placement and device operation. Each tDCS interventionist will thoroughly study these written and video instructions, following which they will practice all procedures. Next, each interventionist must video record head measurement and electrode preparation/placement on six different mock participants. Our tDCS expert's team will review all recordings and issue certification to study staff. If problems in the procedures are discovered, corrective action will be taken (such as additional training or clarification). Additional recordings will then be taken prior to approval.

3.4. Monitoring Intervention Fidelity

3.4.1. Breathing and Attention Training.—To promote consistency and fidelity of the BAT intervention, detailed scripts have been developed to guide implementation of the intervention. All intervention sessions will be video recorded and archived on a secure server. Over the course of the trial, at least 10% of all intervention sessions will be reviewed by our BAT expert and his team to ensure that the intervention is consistent with the script. In addition, during this process the reviewer will categorize the session as either Focused-BAT or Standard-BAT to ensure that the two interventions remain distinct.

3.4.2. Transcranial Direct Current Stimulation.—For each tDCS session, we will capture a 3D scan of participants' head after the electrodes are placed to ensure correct electrode placement using previously published procedures [43]. These photos will be used to create a 3D model of the participant's head that will provide accurate information about where the electrodes were placed.

4. Assessments and Measures

4.1. Primary Outcome Variables

Because this is a proof-of-principle mechanistic trial rather than an efficacy trial, we have three categories of primary outcome variables: clinical pain, QST measures of pain modulatory balance, and brain imaging measures.

4.1.1. Clinical Pain.—The primary clinical outcome measure will be the pain scale from the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC [10] consists of 24 items assessing lower extremity symptoms over the past 48 hours. Respondents report the severity of each symptom on a 5-point scale where higher scores reflect greater symptom severity. The WOMAC yields three subscales: 1) pain during activities (5 items), 2) daytime stiffness (2 items), and 3) impairments in physical function

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(17 items). The WOMAC is widely used in knee OA research, including clinical trials, and has shown adequate construct validity and reliability [11; 49].

4.1.2. Quantitative Sensory Testing.—We hypothesize that our active interventions will improve pain modulatory balance, which would be reflected by improved pain inhibition and reduced pain facilitation [78]. In order to assess this, our primary QST outcome measure will be a composite score that combines conditioned pain modulation (i.e. pain inhibition) with temporal summation (i.e. pain facilitation). Conditioned pain modulation (CPM) will be conducted as in our previous work [69]. Briefly, the test stimulus will be pressure pain threshold assessed (PPT) assessed via algometry (Medoc, Ltd., AlgoMed, Ramat Yishai, Israel) on the left trapezius, and the conditioning stimulus will be right hand immersion in cold water at 12°C (ARCTIC A25 refrigerated bath with an SC150 immersion circulator; ThermoFisher Scientific, USA). PPT will be assessed at baseline, after 30-seconds of cold water immersion, and again immediately after 1-minute of cold water immersion. CPM is computed by subtracting the PPT before immersion from the PPT during immersion, such that higher scores reflect greater pain inhibition.

For temporal summation, a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300 grams of pressure will be applied to the index knee. First, participants will rate the pain intensity experienced during a single application of the monofilament. Then, they will rate the maximum pain intensity experienced during a series of 10 contacts applied at a rate of one contact per second. Temporal summation is computed by subtracting the rating of the single stimulus from the rating of the series of 10 stimuli. When creating the composite pain modulatory balance score, the temporal summation component will be reverse scored, such that higher composite scores reflect healthier pain modulatory balance.

4.1.3. Brain Imaging.—Our primary brain imaging outcome measure will be pain-evoked cerebral blood flow. Specifically, using a 3T Siemens Prisma scanner with a 64-channel head coil, we will perform pseudo-continuous arterial spin labeling (pCASL) with the following parameters: (TR/TE/α = 4s/13ms/90°), labeling time=1.5s, time delay between labeling and imaging = 1.5s. 3.2×3.2mm^2 in-plane resolution, 20 ascending interleaved axial slices of 6mm thickness with 1mm inter-slice gap. 26 dynamic time points are collected in 208s, with pair-wise image acquisition (i.e., control and labeled) for each time point. Two pCASL scans will be performed, one with innocuous stimulation and the other with noxious stimulation, in which mechanical stimuli will be applied for 16 seconds followed by a 16-second rest for the scan duration (as in [37]). This pair of pCASL sequences will be repeated once in order to enhance statistical power. After collecting one pain-evoked BOLD scan and one T1-weighted anatomical scan (see below), these four pCASL scans will be repeated with the participant performing mindfulness meditation. pCASL preprocessing steps will include: motion correction, residual motion effect removing, denoising, registration, spatial smoothing, CBF calculation, and CBF map spatial normalization. Further, based on existing evidence and our preliminary findings we will examine the following regions of interest (ROIs): thalamus, precentral and postcentral cortex, insular cortex, anterior cingulate cortex,

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amygdala, and dorsolateral prefrontal cortex [18; 70]. These ROIs will be selected with the Wake Forest University pick atlas, which uses the Talairach Daemon database [46].

BOLD images will be acquired using an echo-planar imaging (EPI) sequence (TR/TE/α = 1.6s/30ms/70°; multi-band factor of 3 in slice direction; 66 interleaved axial slices with 4-mm-thick slices with no inter-slice gap; 2.5×2.5mm×2.5mm isotropic voxels; 190 repetitions; scan time = 304s). Resting state BOLD scans will be acquired at the beginning of the protocol to determine neural networks supporting pain before and after each respective intervention. Pain-evoked BOLD fMRI scans will be collected with and without mindfulness meditation. Anatomical images will be collected using a high-resolution ($0.8\times0.8\times0.8mm^3$ voxel-size) T1-weighted MP-RAGE sequence that takes 4 minutes 22 seconds. The participant will be performing mindfulness meditation during acquisition of the MP-RAGE scan. BOLD scans preprocessing steps will include the following preprocessing steps using the FEAT module (FSL v6.0): geometric distortions in echo planar images will be corrected using a field map correction method (FSL FUGUE)[7], motion correction (FSL MCFLIRT), interleaved slice time corrected, high-pass temporal filtering, brain extraction (BET), mean global intensity normalization, and spatial smoothing with a 3.2 mm3-D isotropic Gaussian kernel. As previously conducted [80], each subject's anatomical data will be segmented in white matter partial volume maps (FAST algorithm in FSL)[64], white matter values will be extracted (FSL Featquery) and entered in each subject's respective first level analyses as a nuisance covariate of no-interest. Each subject's functional images will be registered to their structural data using a six-parameter linear 3-D transformation and then transformed into standard stereotaxic space [as defined by Montreal Neurologic Institute] using a non-linear boundary bound transformation [34; 44].

4.2. Secondary Outcomes

Additional outcome measures, mediators, moderators and potential covariates for the PROACT Study are presented in Table 2. We will examine treatment effects on several secondary outcome measures, including movement-evoked pain, functional performance, and self-reported disability. To examine the duration of therapeutic responses, we will also collect monthly measures of pain intensity for three months following the intervention.

4.2.1. Short Physical Performance Battery (SPPB).—The SPPB is a widely used measure of lower extremity mobility and function, comprised of three different components: standing balance tasks (side-by-side, semi-tandem, and tandem stance), a 4-meter walking speed task, and a repeated chair stand task [35; 36]. The SPPB has been extensively validated and used for assessing lower extremity function among middle aged and older adults [24; 54], including those with knee OA [38; 62]. Scores on each component range from 0 (worst performance) to 4 (best performance), and these are summer to create a total score ranging from 0 (worst performance) to 12 (best performance). In addition, in order to assess movement-evoked pain, we will ask participants to rate the pain they experienced during each task using a numerical 0–100 numeric rating scale (0 = no pain, 100 = the most intense pain imaginable), as in our prior studies [13; 19].

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4.2.2. Disability and Follow-Up Measures.—The WOMAC Physical Function Scale will be used to assess changes in self-reported disability following the intervention. Also, follow-up measures of pain intensity and interference will be collected using the items from the Graded Chronic Pain Scale [75], administered online or via telephone each moth for three months after treatment.

4.3. Moderators and Mediators of Change

Ethnic/race Group.—We hypothesize that ethnic/race group will moderate treatment effects, in that the active treatments will be more effective for NHB compared to NHW adults with knee OA. Participants will report their self-identified ethnicity (Hispanic or Latino/a versus non-Hispanic or Latino/a) and race using the United States Office of Management and Budget minimum standards. For eligibility, individuals must self-report as non-Hispanic or Latino/a and either White or Black/African American.

Mediators.—Potential mediators of treatment-induced changes in clinical pain will include changes in pain modulatory balance (assess via QST), as well as changes in pain-evoked regional cerebral blood flow, as described above. In addition, treatment-induced changes in perceived stress and pain catastrophizing will be examined as potential mediators of changes in clinical pain. Perceived stress will be assessed using the Perceived Stress Scale, a 10-item instrument that assesses individuals' subjective level of stress related to different types of life stress and has documented validity and reliability [16; 17]. A total score is derived by summing all items, with higher scores indicating greater perceived stress. Catastrophizing will be assessed using the Pain Catastrophizing Scale, a 13-item questionnaire assessing three components of catastrophizing: rumination, magnification, and helplessness [66]. Abundant evidence links pain catastrophizing with poorer pain-related adjustment [67] and a mindfulness intervention has been shown to reduce pain catastrophizing [71].

5. Safety Monitoring

We will use a centralized online system for safety monitoring, including tracking and reporting of adverse events (AEs). Before and after each intervention session, participants will complete a questionnaire assessing symptoms that may represent adverse events resulting from study procedures, including the tDCS and/or BAT interventions. Study staff will submit information regarding AEs using an electronic AE submission form, which will include information regarding seriousness, expectedness and relatedness of the AE. Reporting of AEs will follow all applicable NIH and IRB guidelines. The PROACT Study will empanel a four-member Data and Safety Monitoring Board (DSMB), which will review study progress and AEs in order to monitor the risk-benefit ratio of the trial. Twice per year, the DSMB will receive a report that details progress with recruitment and retention, data completeness and quality, AEs, and any other reportable events. The study team and study sponsor will meet with the DSMB to review the report, and the DSMB will issue its findings and recommendations to the study sponsor.

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6. Data Management & Analysis

6.1. Online Data Management System.

A REDCap online data management system will be used for PROACT. This secure system is accessible by both data collection sites and allows online administration of questionnaires to participants, including automation of emails to study participants for this purpose. The system also includes range limits to enhance accuracy of data entry by participants and study staff. The system will also generate reports for monitoring of enrollment, retention, and other important study metrics. The REDCap system is maintained at the UF site.

6.2. Sample Size and Statistical Power

We plan to randomize 360 individuals to four groups defined by a 2X2 factorial design, and we expect to have 320 completers. Table 3 illustrates the effect sizes (Cohen's D) produced by the proposed interventions compared to their sham conditions for different outcomes that have been reported in previous studies [1; 80]. We have powered to perform six primary hypothesis tests (sham (Standard) vs real (Focused) BAT and Sham vs. Real tDCS for three primary outcomes) with the use of linear contrast test at a Bonferroni corrected α=0.0083 significance level. Even with this conservative approach, the proposed sample size provides sufficient power for detecting single intervention effects, with power greater than 90% for most outcomes. We do not have effect size estimates for the combined effect, but our sample size provides 80% power to detect effects as small as Cohen's D=0.39.

6.3. Statistical Analysis Plan

Summary statistics will be calculated by group for demographic characteristics and all predictor and outcomes measures at baseline and follow-up. Statistical inference will be conducted for the three primary aims as follows.

6.3.1. For Aim 1, we will test the effects of BAT, tDCS, and their interaction upon outcomes. For hypotheses 1a-1c, our primary outcomes will be pain modulatory balance (ratio of CPM to temporal summation), pain-evoked cerebral activation, and clinical pain, respectively. Intention-to-treat analysis will be conducted using appropriate linear contrasts to test for intervention effects accounting for interaction terms based on general linear models with covariate adjustment for site, sex, age, and baseline value. Specifically, for each outcome (Y), the model will be:

$$E(Y) = \beta_0 + \beta_1 BaselineScore + \beta_2 Covariates + \beta_3 BAT + \beta_4 tDC + \beta_5 NHB + B_6 BAT * tDCS + \beta_7 BAT * NHB + \beta_8 tDCS * NHB + \beta_9 BAT * tDCS * NHB.$$

6.3.2. In this model, BAT and tDCS are dummy variables for interventions, NHB is the dummy variable for non-Hispanic Blacks. Linear contrasts will be employed to test the main effects of BAT (corresponds to the test of $\beta_3 + \beta_6/2 + \beta_7/2 + \beta_9/4=0$) and tDCS (test of $\beta_4 + \beta_6/2 + \beta_8/2 + \beta_9/4=0$). These six tests (2 main effects for three primary outcomes) will be performed at one-sided α=0.0083 significance level. In addition, point estimates and 95% confidence

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intervals will be obtained for the BAT and tDCS effects with or without the presence of the other treatment in the whole population or within NHB and NHW subgroups. We will use normal probability plots to assess distributional assumptions of the models. The above analysis plan will be followed for other outcomes including resting state cerebral blood flow, disability and functional performance, as well as the analysis of changes of the outcomes from post-treatment to three-month follow-up. For Aim 2, we will assess interactions between ethnicity/race and intervention. Point estimates and 95% confidence intervals will be obtained for the ethnic/race difference in the effects of BAT and tDCS on each outcome. Because we expect the interaction effect to be smaller than the main effect, for formal hypothesis testing, we plan to pool evidence across three primary outcomes to test the ethnic group differences. Specifically, we will obtain a p-value corresponding to test the hypothesis $\beta_7=\beta_8=\beta_9=0$ for each outcome based on the general linear model specified in the analysis plan for Aim 1. And Fisher's combination of three p-values will be used as the overall test statistic, which will be compared to the null distribution obtained through permutation of ethnic group variable.

6.3.3. For Aim 3, path models with strictly ordered relationships will be used to study the interventions' direct effects on clinical pain and disability and the indirect effect on the mediating variables including pain modulatory balance; resting state and stimulus-evoked pain-related brain function; perceived stress, pain catastrophizing, and mindfulness. We will construct additional analyses using pre-treatment variables as predictors of intervention effects. We will examine separate multivariable models for each ethnic group to determine whether mediators of treatment effects differ for NHBs vs. NHWs.

6.3.4. We will consider multiple covariates in our models to control error variance and reduce confounding. Study site will be included as a covariate to control for between-site variability in predictors and outcomes. Also, we will consider sociodemographic factors, including sex, age, education and income as covariates. These potential covariates will only be included in the model if they show a bivariate association with the outcome variable being analyzed in the model.

6.4. Missing Data and Sensitivity Analysis.

The four randomized groups will be compared in missing patterns in the primary outcomes including reasons for missing data, timing of missing data, and distributions of baseline covariates and earlier outcomes. We will consider the following approaches to impute each of the primary outcomes: (1) the last-observation-carried-forward method; (2) missing primary outcome predicted by a fitted regression model using demographic an baseline clinical variables; (3) missing primary outcome predicted by baseline and available follow-up outcomes on a fitted regression model. The imputation method for the primary intent-to-treat analysis will be selected using cross-validation performed on the participants with complete data. Specifically, we will evaluate imputation accuracy based on 2,000 repetitions that randomly leave out 20% of the complete samples. In addition, to consider the

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uncertainty due to missing values, we will apply the SAS multiple imputation procedure to generate multiple imputed data sets using the selected imputation approach, and combine results from analyses of these data sets, e.g., to provide mean and variance of the treatment effect estimates. No imputation is planned for secondary outcomes. Missing data in secondary outcomes will be considered missing. For a subject to achieve a given secondary endpoint, that endpoint must be observed.

7. Discussion

Osteoarthritis represents the leading cause of pain and disability among older adults, and existing treatments fail to adequately reduce pain and improve function for a large proportion of OA sufferers [56; 63]. Abundant evidence reveals clinically important ethnic and racial disparities in OA-related symptoms, with NHB adults experiencing greater pain and disability compared to their NHW counterparts [3; 73]. In addition to the multiple societal and health system factors that contribute, increasing evidence implicates a variety of biological and psychosocial processes as potential drivers of these disparities. In particular, our recent findings suggest that altered pain modulatory function as well as higher levels of stress and cognitive-attentional factors may promote greater pain and disability among NHB adults with knee OA [13; 20; 39]. Thus, we have designed a mechanistic, proof-of-principle clinical trial to test the central hypothesis that ethnic/racial differences in psychosocial stress and pain-related cognitive-attentional processes adversely impact pain-related brain structure and function and perturb pain modulatory balance among NHBs relative to NHWs, producing greater OA-related pain and disability among NHBs. Specifically, we will test the combination of BAT, a mindfulness meditation intervention targeting attention and stress, and tDCS, a treatment targeting central pain processing. While these individual treatments have shown pain relieving effects in musculoskeletal pain [1; 15; 55; 74], this will be the first attempt to investigate the potential additive or synergistic effects of these interventions when combined.

Considerable evidence demonstrates clinical efficacy of mindfulness meditation and tDCS for individuals with chronic pain when delivered individually. Mindfulness-based interventions have demonstrated effectiveness for treating multiple musculoskeletal pain conditions [15; 74], including among older adults [55]. Indeed, meta-analyses suggest that mindfulness-based interventions produce significant improvements in pain, with effect sizes ranging from small to large [30; 40]. In contrast to many previous efficacy trials, we propose to use a brief mindfulness intervention in our mechanistic, proof-of-principle trial. Our BAT intervention involves approximately 100 minutes of total treatment time and includes instructions for participants not to practice outside of the clinical visits. This intervention is patterned after the protocol designed by Zeidan and colleagues [81; 82], which significantly improves: a) behavioral pain ratings, b) cognitive control, c) affective regulation, and attenuates pain-related brain activation through novel pain modulatory neural mechanisms [80–82; 84]. Regarding tDCS, recent meta-analyses demonstrate significant effects on chronic pain intensity, with effect sizes that are moderate and clinically significant [57; 72]. In the first trial of tDCS among adults with knee OA, Ahn and colleagues [1] showed that a five-day course of active tDCS significantly reduced knee pain intensity compared to sham, and the pain reduction lasted at least three weeks. Thus, each of our interventions alone has

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shown efficacy in people with chronic pain; however, no previous study has tested whether the two interventions combined produce additive or synergistic effects.

Our hypothesis that these interventions will be more effective when combined is based on several lines of existing evidence. First, the BAT and tDCS interventions target pain-related cognitive-attentional and cerebral processes, respectively; therefore combining two interventions that influence separate mechanisms should increase the therapeutic efficacy. Second, tDCS is well-recognized as a non-invasive approach to induce neuroplasticity, increasing the brain's ability to adaptively reorganize in response to psychological or behavioral interventions [42; 86]. Because the therapeutic effects of mindfulness are at least in part due to adaptive changes in pain-related brain function (i.e. neuroplasticity) [14; 65], applying tDCS concurrent with BAT may augment the adaptive brain changes induced by BAT. This approach of combining tDCS with cognitive and behavioral interventions is being tested in other clinical populations, including patients with cognitive or motor impairment [41; 77] and major depression [9]. Of direct relevance to the current trial, a recent study in healthy young adults showed that tDCS combined with brief cognitive therapy produced larger increases in heat pain tolerance than either treatment alone, showing promise for combining tDCS and a cognitively-based pain intervention [61]. Similarly, tDCS targeting the right dorsolateral prefrontal cortex was found to increase conditioned placebo and nocebo responses using experimental heat pain, suggesting that tDCS can potentiate cognitively-mediated pain modulation [25]. While no previous study has tested whether combined tDCS and mindfulness are superior to either intervention alone, a recent pilot trial tested the feasibility of a home-based mindfulness intervention combined with active tDCS compared to the combination of sham-mindfulness and sham-tDCS among older adults with knee OA [2]. The findings showed that the combined intervention was feasible, and the active treatment condition produced greater pain reductions than the sham condition. The factorial design implemented in the current trial will permit a systematic evaluation of the independent and combined effects of these two interventions, including the potential for synergistic effects of tDCS plus BAT.

The proposed trial emerged from our prior research exploring ethnic/race disparities in OA-related pain and disability; therefore, an important goal is to investigate the potential moderating influence of ethnicity/race on the effects of these interventions. While ethnic/race disparities in pain have been widely documented [6; 33; 73], efforts to reduce these disparities through targeted interventions have been limited. Considerable research has identified important societal and health system factors that contribute to the greater burden of pain among minority groups, including socioeconomic challenges, inadequate access to health care, and biases in provision of pain treatment [6; 33; 60]. Though critically important, intervening on these complex systemic and societal factors represents a daunting and long-term undertaking. In the near term, a more feasible strategy might be to target more proximal intra-individual processes that may contribute to disparities in pain. In this regard, previous work implicates psychosocial stress and cognitive-attentional processes as potential contributors to the greater pain and disability experienced by NHB adults with knee OA. For example, NHB women with arthritis reported lower arthritis-related stress but greater chronic life stress than their NHW counterparts, and both arthritis stress and chronic life stress were associated with greater pain and disability among NHB women [50]. More

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recently, Booker and colleagues reported that NHB and NHW adults with knee OA reported similar levels of perceived stress; however, perceived stress was more strongly associated with movement-evoked pain in NHBs [13]. Regarding cognitive-attentional processes, NHBs reported higher levels of pain vigilance compared to NHWs, and pain vigilance predicted greater OA-related pain and disability [39]. Also, multiple studies have observed higher levels of pain catastrophizing among NHBs versus NHWs [51; 52], which have been found to mediate ethnic/race group differences in clinical pain [26; 47] and experimental pain sensitivity [28; 52; 53]. In addition to these psychosocial contributors, our previous work demonstrates impaired pain modulatory balance among NHBs, which is associated with increased OA-related pain [22]. These findings support our premise that interventions targeting stress and cognitive-attentional processes (i.e. BAT) as well as central pain processing (i.e. tDCS) will help reduce ethnic/race disparities in OA-related pain and disability.

This mechanistic, proof-of-principle trial will determine whether a brief course of mindfulness and tDCS, alone and in combination, reduces clinical pain and improves central pain processing in adults with knee OA. Further, we will test whether these interventions produce greater benefit in NHB adults, thereby reducing ethnic/race disparities in OA-related pain. This represents perhaps the first clinical trial designed to reduce disparities in pain by targeting specific biological and psychosocial mechanisms using non-pharmacologic pain treatments. In addition to examining clinical outcomes, this trial will provide novel experimental information regarding the mechanisms underlying ethnic/race group differences in responses to pain and its treatment, opening the door to future tailoring of pain treatments for NHBs and NHWs experiencing OA and other chronic musculoskeletal pain conditions.

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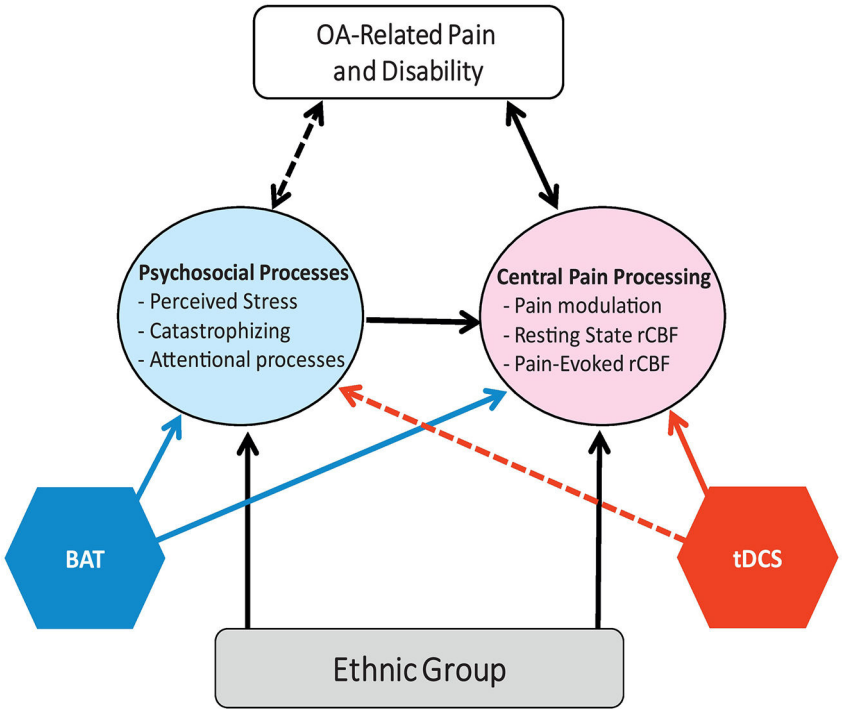

Figure 1. Heuristic Model of Ethnic Differences in OA-Related Pain and Disability and Proposed Treatment Effects.

Our model posits that ethnic group differences in psychosocial stress and cognitive-attentional processes negatively impact central pain processing, reflected by altered resting state and pain-evoked brain function and pain modulatory imbalance, leading to greater OA-related pain and disability among African American adults. We propose that transcranial direct current stimulation (tDCS) will have direct effects on central pain processing and indirect effects on psychosocial processes. Our mindfulness intervention, Breathing and Attention Training (BAT) will directly impact both psychosocial processes (including stress and pain-related cognitive-attentional processes) and central pain processing. Importantly, we believe that neuroplastic benefits of tDCS will potentiate the ability of BAT to produce adaptive changes in pain-related brain function. Note: dashed line = indirect effect.

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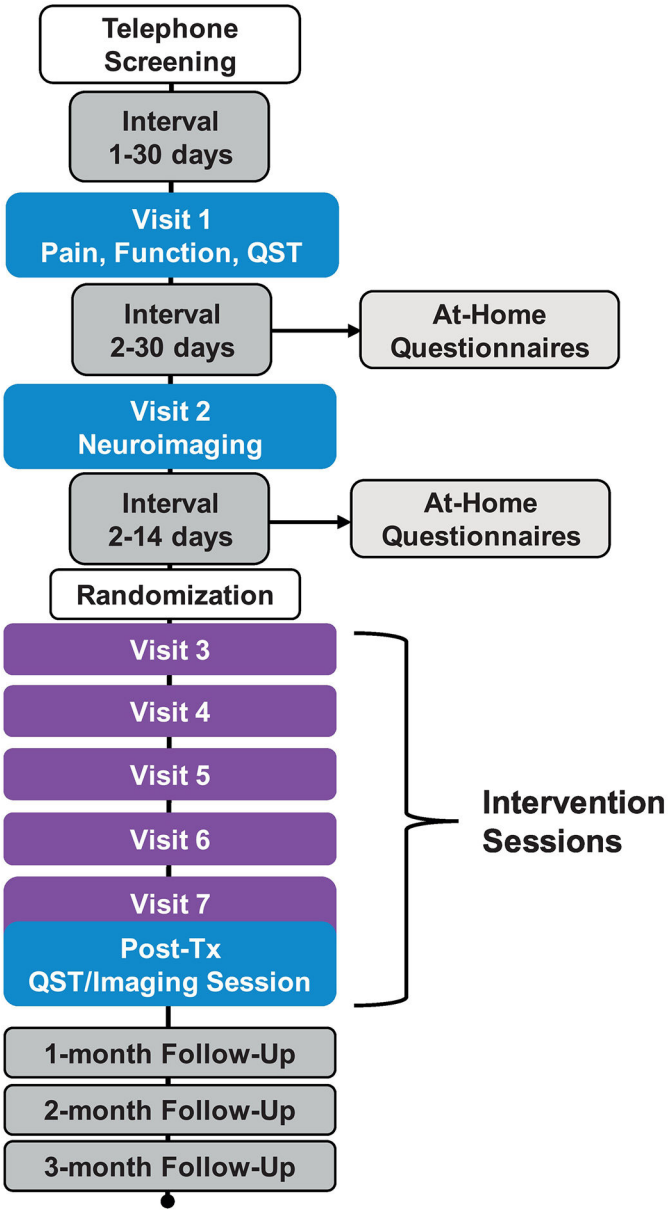

Figure 2. Protocol Timeline.

The figure presents the protocol flow for each participants, including screening, baseline assessments (Visits 1 & 2), intervention visits (Visits 3–7), post-treatment assessment (Visit 7), and three monthly follow-up assessments.

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Table 1.

Participant Protocol Timeline

	Baseline			Treatment				Monthly Follow-Up		
Study Activities	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**1-Month**	**2-Month**	**3-Month**
Informed Consent	X									
Baseline Questionnaires	X	X								
Activity Tests	X						X			
Sensory & Pain Tests	X						X			
Brain Imaging		X					X			
Treatment Questionnaires							X			
Treatment Session			X	X	X	X	X			
Pain Assessment			X	X	X	X	X			
Follow-Up Questionnaire								X	X	X

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Table 2.

Outcome Measures, Mediators, Moderators and Covariates

Category	Primary Outcomes	Secondary Outcomes	Mediators[a], Moderators, Covariates
Clinical Pain & Function	WOMAC Pain	GCPS Pain Movement Evoked Pain	
Pain Modulation	CPM:TS Ratio		CPM:TS Ratio
Neuroimaging	Pain-Evoked rCBF	Resting rCBF	Pain-Evoked rCBF
Function		SPPB WOMAC Function GCPS Interference	
Demographic			Moderator: Race/Ethnic Group Covariates: Study Site, Sex, Age, Education, Income
Psychological			Mindfulness Perceived Stress, Stress

[a]-Mediators include baseline levels and treatment induced changes in the listed variables.

WOMAC=Western Ontario McMaster Universities Osteoarthritis Index; CPM=Conditioned Pain Modulation; TS=Temporal Summation; rCBF=Regional Cerebral Blood Flow; GCPS=Graded Chronic Pain Scale; SPPB=Short Physical Performance Battery

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Table 3:

Effect Sizes Observed for tDCS and BAT based on Previous Research

		Power for Different Sample Sizes		
Outcome	**Cohen's D**	**N = 300**	**N = 320**	**N = 340**
tDCS (from [1]**)**				
CPM	0.34	0.61	0.65	0.68
Clinical Pain Rating	0.44	0.88	0.90	0.92
BAT (from [74]**)**				
Heat Pain Rating	0.51	0.97	0.98	0.99
rCBF	0.82	0.99	0.99	0.99