Protocol

1. Project Title: **Pain Relief for OsteoArthritis through Combined Treatment (PROACT)**
Ethnic Differences in Responses to Painful Stimuli (Grant Title)

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3. Abstract:

Osteoarthritis (OA), is the leading cause of pain and disability in older adults, and OA disproportionately affects African Americans (AAs). Our UPLOAD (**U**nderstanding **P**ain and **L**imitations in **O**steo**A**rthritic **D**isease) Study has demonstrated significantly greater pain and disability among AA adults with knee OA compared to their non-Hispanic white (NHW) counterparts. Moreover, we observed an altered pain modulatory profile, characterized by greater pain facilitation and diminished pain inhibition, among AAs (1, 2), and emerging findings from UPLOAD-2 implicate brain structure and function as potential mediators of the greater burden of OA-related pain among AAs. Also, we have identified pain-related psychosocial (e.g. pain catastrophizing, environmental stress) risk factors that contribute to ethnic group differences in clinical pain and altered central nervous system pain processing (3). These results support our scientific premise that ethnic 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 AAs compared to NHWs, leading to greater OA-related pain and disability among AAs. Hence, treatments that target these psychosocial and brain mechanisms will reduce OA pain and disability. No investigator to date has determined whether treatments that target brain function and pain-related psychosocial processes can reduce ethnic differences in clinical symptoms and altered central pain processing in OA. In this regard, we recently completed a pilot trial demonstrating that a brief course of transcranial direct current stimulation (tDCS) significantly improved pain in adults with knee OA (4); however, this study was not designed to examine differences in treatment outcome among AAs and NHWs. Because tDCS promotes neuroplasticity, it may be particularly effective when combined with a psychological treatment for pain that also stimulates adaptive changes in the brain, such as mindfulness interventions (5, 6). Therefore, we propose to test whether a five-day course of mindfulness meditation, referred to as 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 AAs and NHWs with knee OA. This approach will provide experimental evidence supporting our scientific premise and will produce the first evidence of ethnic group differences in response to these potentially synergistic nonpharmacologic pain treatments.

4. Background:

Osteoarthritis (OA) is the leading cause of pain and disability among older adults (7, 8), 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 (9). Racial and ethnic group differences in OA-related pain and disability have been widely reported. African American (AA) adults with knee OA experience greater pain and disability than their non-Hispanic white (NHW) counterparts (1, 10-12). Our previous and ongoing work in the UPLOAD Study has been focused on elucidating the mechanisms underlying these racial and ethnic disparities in OA pain. Specifically,

based on increasing evidence that altered central pain processing contributes importantly to pain and disability in knee OA (1, 13-15), we have exploited quantitative sensory testing (QST) and neuroimaging methods to characterize central pain processing in AAs and NHWs with knee OA. We have observed ethnic group differences across multiple QST measures (see (1, 2, 16)), with a pattern of results suggesting enhanced pain facilitation and impaired pain inhibition (i.e. pain modulatory imbalance) among AAs relative to NHWs. In addition, previous neuroimaging studies have demonstrated altered pain-related brain structure and function among adults with knee OA compared to controls (17, 18), and during the current cycle we have extended these findings, showing ethnic group differences in pain-related brain structure and function among adults with knee OA.

Biopsychosocial Mechanisms Underlying Ethnic Disparities in OA Pain: Multiple biopsychosocial processes contribute to the greater burden of OA-related pain among AA compared to NHW adults with knee OA. As noted above, altered central pain processing represents one potentially important contributor, as our previous QST results reveal altered pain modulatory balance (i.e. greater pain facilitation and lower pain inhibition) among AAs with knee OA (1, 2, 16). Moreover, our preliminary findings demonstrate ethnic group differences in pain-related brain structure and function, which may contribute to the greater clinical pain among AA adults with knee OA. We have also identified important psychosocial contributors to the observed ethnic differences in pain and disability. Specifically, AA individuals with OA reported higher levels of pain-related vigilance and pain catastrophizing (19, 20), suggesting that pain-related cognitive and attentional processes contribute to greater pain and disability among AAs. In addition, AAs experience greater levels of environmental and psychosocial stress (e.g. discrimination) than NHWs (21, 22), further elevating their risk for increased OA-related pain and disability. In addition, perceived stress is associated with increased experimental pain sensitivity and OA-related pain and disability in both ethnic groups. Taken together, these findings support our scientific premise that ethnic group differences in psychosocial stress and cognitive-attentional processes negatively impact central pain processing, reflected by altered pain-related brain structure and function and unhealthy pain modulatory balance, leading to greater OA-related pain and disability among AAs. However, experimental evidence supporting this premise is lacking; therefore, we propose to directly modulate these processes using treatments that target these psychosocial and brain mechanisms. We anticipate that these interventions will reduce stress and pain catastrophizing, improve pain-related brain function, and restore pain modulatory balance, thereby reducing OA pain and disability and ethnic differences therein.

Rationale for Testing BAT, tDCS and Their Combined Effects: We plan to test whether a five-day course of BAT (vs. sham) and tDCS (vs. sham), and their combination, will enhance pain modulatory balance and pain-related brain function, reduce clinical pain, and attenuate ethnic differences therein, among AAs and NHWs with knee OA. We have selected these treatments for several reasons: 1) Both Represent Brain-Based Interventions that Target Our Mechanisms of Interest: Mindfulness improves stress responses by targeting attentional processes and reducing maladaptive cognitive appraisal of internal and external events (23). Indeed, mindfulness has been shown to reduce pain sensitivity and adaptively modulate pain-related brain function (5, 24), diminish self-reported stress and physiological stress reactivity (25), reduce pain catastrophizing (26), and enhance attentional control (27). tDCS directly impacts brain function by altering neuronal excitability (28) and can adaptively modulate pain modulatory balance (29) and pain-related brain function (30). Notably, a recent preclinical study demonstrated that tDCS prevented development of stress-induced hyperalgesia in rats, suggesting that tDCS may be particularly effective against stress-related changes in pain processing (31). 2) Both Are Effective in Treating Chronic Musculoskeletal Pain: Mindfulness-based interventions have demonstrated effectiveness for treating multiple musculoskeletal pain conditions (32, 33), including among older adults (34). Similarly, tDCS shows beneficial effects in patients with musculoskeletal pain (35, 36), including a recent pilot study showing significant effects on pain and sleep among older adults with chronic pain (37). 3) We Have Experience with Brief Protocols for Both Interventions: The four-day mindfulness training intervention produced analgesia that was greater in magnitude and mediated via distinct neural mechanisms compared to a credible sham mindfulness condition (5, 24).

Mindfulness-induced analgesia was associated with decreased activation in brain regions subserving pain perception and increased activation in brain regions involved in cognitive pain modulation (5, 24). In addition, in collaboration with Dr. Brian Ahn (University of Texas Health Science Center), we recently conducted a pilot clinical trial testing a 5-day course of active versus sham tDCS in patients with knee OA. Compared to the sham condition, active tDCS produced significant reductions in clinical pain severity with large effect sizes (4). 4) Combined tDCS and BAT May Produce Additive or Synergistic Effects: 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 (38, 39). Because the therapeutic effects of mindfulness are at least in part due to adaptive changes in pain-related brain function (i.e. neuroplasticity)(40, 41), applying tDCS concurrent with BAT may augment the adaptive brain changes that occur with 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 (42-44). Indeed, 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 (45).

5. Hypotheses and Specific Aims:

Based on our scientific premise, we propose to address the following Specific Aims (SA) and hypotheses.

SA1: 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 OA-related pain and disability among AA and NHW adults with symptomatic knee OA.

Hypothesis 1: Compared to the combination of sham BAT and sham tDCS, both tDCS and 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 combined treatments will produce the largest effects, showing evidence of additivity or even synergy.

SA2: 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 AA and NHW adults with symptomatic knee OA.

Hypothesis 2: Real BAT and tDCS, independently and in combination, will produce: 1a) Greater improvements in pain modulatory balance among AAs compared to NHWs; 1b) Greater decreases in resting and pain-evoked cerebral blood flow in pain-related ROIs among AAs compared to NHWs; and 1c) Greater improvements in clinical pain, self-reported disability, and functional performance among AAs compared to NHWs. We anticipate that the combined treatments will produce the largest benefits for AAs compared to NHWs. We expect more robust treatment effects among AAs, as our previous findings suggest that the risk factors targeted by these treatments produce greater adverse consequences among AAs with knee OA.

SA3: To identify biopsychosocial predictors and mediators of treatment-related improvements in clinical pain and disability following BAT and tDCS among AAs and NHWs with symptomatic knee OA.

Hypothesis 3: 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 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 AAs vs. NHWs.

6. Research Plan:

Table 1. Treatment Conditions

	Real tDCS	Sham tDCS
Real BAT	90 Adults (45 AA, 45 NHW)	90 Adults (45 AA, 45 NHW)
Sham BAT	90 Adults (45 AA, 45 NHW)	90 Adults (45 AA, 45 NHW)

D1. Overview: We propose a brief proof-of-principle, mechanistic trial to determine whether interventions that target cognitive pain modulation (BAT) and pain-related brain networks (tDCS) will normalize pain modulatory balance and pain-related cerebral activation, thereby reducing clinical pain and disability, and ethnic differences therein. In a fully factorial design, we will randomize 360 adults (180 AA, 180 NHW) with knee OA to one of four conditions created by crossing Real tDCS vs. Sham tDCS with Real BAT vs. Sham BAT (**Table 1**). This is a two-site study conducted at the University of Florida (UF) and the University of Alabama at Birmingham (UAB). Equal numbers of participants will be recruited at each site. At the UF site we will offer protentional participants the option of the study team arranging travel to the study site via Uber Health. Using the REDCap randomization module, we will block randomize with stratification for site, sex, and race in double blind fashion. After initial eligibility screening, each participant will complete two baseline assessments, including clinical measures, QST, and neuroimaging. After being randomized to one of the four treatment conditions, participants will undergo a five-day intervention period. On the last intervention day after the final treatment, participants will undergo post-treatment clinical, QST and brain imaging assessments. The timing of study activities throughout the protocol is depicted in **Table 2**. In order to assess persistence of treatment effects, participants will complete follow-up online or telephone assessments of clinical pain and disability each month for three months after completion of treatment.

Participants will be paid up to $350 for completing the entire protocol, which is itemized as follows:

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

- Baseline Session 1 ($50)
- Baseline Questionnaires ($20)
- Baseline Session 2 ($50)
- Visits 1 – 4 ($25 each)
- Visit 5 ($75)
- Travel allowance ($25)
- Follow-Up Questionnaires ($30)

This reimbursement is comparable to what others at these institutions provide participants for studies of this nature, based on the time commitment and number of sessions.

D2. Intervention Design: We propose a proof-of-principle randomized trial to demonstrate that interventions targeting pain-related psychosocial processes, pain modulatory imbalance and altered brain function will be effective for OA pain and will reduce racial disparities in OA pain and disability. This is not an efficacy trial, rather we are considering these interventions as experimental manipulations of the biopsychosocial mechanisms that we believe are driving ethnic group differences in OA-related pain and disability. While we expect clinical outcomes to improve, our primary

mechanistic interest is in capturing changes in brain function and pain modulatory balance induced by the interventions. Thus, this research includes aspects of Stage 0 (basic science to inform intervention development) and Stage 1 (modification and refinement of existing interventions) intervention development (50). Subjects. A total of 360 individuals with knee OA (180 AA, 180 NHW) will be enrolled in the study. We anticipate a 10% attrition rate, given the brief duration of the intervention, which will yield a final sample size of at least 320 participants. In our pilot trial of tDCS, attrition was much lower (2.4%)(4); however, in this larger two-site study, we account for the possibility of increased attrition. As during the current funding cycle, both community-based and clinic-based recruitment methods will be utilized at both study sites with similar inclusion-exclusion criteria as in our prior and ongoing work. Initial Screening. All participants will undergo a knee OA screening interview that shows 87% specificity and 92% sensitivity for detecting knee OA (51). The screening will also assess demographic and health history information to ensure that no exclusion criteria are present. Eligible individuals will be scheduled for baseline assessment at the study site. Demographic Measures. Ethnic group will be determined by participant self-report using the standard Health and Human Services categories. We will recruit adults who self-identify as either Black/African American or non-Hispanic white (NHW) as their primary ethnic/race group. Socioeconomic Status (SES): Because ethnic/race groups often differ in SES (52), and lower SES has been associated with increased risk of clinical pain (53, 54), including increased prevalence of arthritis (55, 56), we will obtain measures of SES.

D2.1. Baseline Assessment: Two baseline visits will occur in the six weeks before the intervention. The first baseline session will assess: health history, cognitive function, clinical pain and function and QST measures. The second baseline session will involve brain imaging. In order to distribute participant burden, some questionnaires will be completed online between the first 3 sessions, while others will be completed during the two pre-treatment sessions. The following questionnaires will be completed during the pre-treatment phase of the protocol.

Socioeconomic status (SES): Using address information provided by the participant, we will access publicly available online tools that allow us to derive geographically-based metrics, such as the area deprivation index (ADI)[58], as well as measures of residential segregation and potentially other census-based measures that reflect social determinants of health and poverty.

Literacy Testing: We will conduct a brief test to measure the participant's ability to read common medical words (the REALM-R [11]), in order to determine whether the participant may need assistance with completing questionnaires.

Clinical Pain and Function: In order to determine the effects of the intervention on pain, we will assess clinical pain at the beginning and end of each intervention study visit with Numerical Rating Scale (NRS) assessing current pain from 0 (no pain) to 100 (most intense pain imaginable), as in our previous pilot trial (4). In addition, at baseline and post-treatment we will also assess clinical pain and self-reported function using the following symptom questionnaires: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[12], which will be our primary clinical measure, and the Graded Chronic Pain Scale. To assess functional performance pre- and post-treatment, the Short Physical Performance Battery (SPPB) will be completed. This measure is widely used in older populations to assess lower extremity function (58, 59).

Psychosocial Measures: We will ask participants to complete the following questionnaires that assess pain-related psychosocial factors: the Pain Catastrophizing Scale (PCS) consists of 13 items assessing three components of catastrophizing: rumination, magnification, and helplessness (61); the Perceived Stress Scale (PSS)-14 is a 14-item instrument that assesses individuals' subjective level of stress related to different types of life stress and has documented validity and reliability (64, 65); the Freiburg Mindfulness Inventory (FMI) will be administered to assess mindfulness at baseline and following treatment (66). In order to examine additional clinical and psychosocial factors that may predict treatment response, we will also administer: the Positive and Negative Affect Scale (PANAS, State and Trait versions), the PROMIS Sleep disturbance 8b & Sleep Related Impairment questionnaires, and the MoCA.

Resilience Measures: In order to investigate whether resilience predicts responses to our interventions, we will administer several pre-treatment resilience measures. These include: the Pain Resilience Scale, the PROMIS Positive Affect & Well-Being Scale, PROMIS Support Scale, the Life Orientation Test-Revised, the Adult Hope Scale, and the PROMIS Sleep Disturbance Scale 8a.

Post-treatment measures of clinical pain/function, QST measures, and brain imaging will be re-assessed after the final intervention session. In order to accommodate participant and clinic schedules, some participants will complete these measures on Day 5, immediately after the intervention. For other participants, some or all of the measures may be completed in a separate session within a few days of the final intervention.

Baseline Session 1

Quantitative Sensory Testing**:** In order to determine pain modulatory balance, all participants will undergo assessment of mechanical pain and conditioned pain modulation (CPM). Mechanical Pain Procedures: Pressure pain threshold (PPT) will be assessed on the most painful knee and at up to two unaffected sites ipsilateral to the tested knee, the quadriceps muscle and the trapezius muscle. The examiner will apply a constant rate of pressure and the participant will be instructed to indicate when the sensation first becomes painful. Also, punctate mechanical stimuli will be delivered to the knee and the hand using von Frey hairs, which are nylon monofilaments. This test will involve delivering either one stimulus or a series of 5-10 repeated stimuli and asking participants to report the intensity of pain and unpleasantness experienced. Conditioned Pain Modulation: As a measure of pain inhibition, we will test the ability of cold water applied to one hand to diminish the experience of pressure pain on the contralateral trapezius. First, pressure pain threshold will be measured on the trapezius as described above. Then, the participant will immerse his/her opposite hand in a cold water bath at a temperature ranging from 10-12 °C. Subjects will immerse their hand and will report when they first feel pain, then will continue for up to 1 minute or until they wish to stop (whichever comes first). Subjects will be prompted to rate the intensity of the cold-pressor pain at pre-determined times during the test. Approximately thirty seconds into the cold water immersion, pressure pain threshold will again be measured. Upon hand withdrawal, the pressure pain test will be repeated.

Baseline Session 2

In order to reduce costs and permit enrollment of participants in whom neuroimaging may be contraindicated, we plan to conduct neuroimaging in approximately two-thirds of the sample. This is justified, as the effect size for intervention-induced changes in neuroimaging outcome measures is notably larger than for QST and clinical outcomes (see Table 4 below). The participants who will not undergo neuroimaging will be identified as follows.

1) Individuals who meet eligibility criteria but are unable to complete imaging due to a contraindication (e.g. claustrophobia, metal implants, body size). We anticipate that this will account for the majority of participants that do not complete neuroimaging.
2) Individuals for whom we are unable to schedule time in the MRI scanner based on the participant's availability, scanner availability, and/or staff availability.
3) If the first two considerations do not account for enough participants, we will randomly select some individuals who will not complete neuroimaging.

In order to ensure that the proportion of participants completing neuroimaging is equal across the four intervention conditions, we will monitor these proportions on a regular basis. If imbalances emerge, we will incorporate neuroimaging status into our randomization scheme.

Brain Imaging Measures: A multimodal imaging protocol will be conducted both before and after the intervention period in order to examine functional and structural connectivity, structural changes, and cerebral responses to evoked pain. Before conducting imaging, all participants will complete the MRI Screening Form to ensure that there are no contraindications. The MRI is not

mandatory for subject completion and will not be done in participants who are claustrophobic or have other contraindications. We will use resting state (RS)-fMRI to evaluate baseline functional connectivity between brain regions associated with pain processing. During resting state, all subjects will be asked to keep their eyes closed. Connectivity will be examined in different regions of the pain processing system as well as in previously described networks (e.g. the default mode network).

Standard BOLD-fMRI and/or arterial spin labeling will be used to determine changes in regional cerebral blood flow to painful mechanical stimuli applied to the knee of participants. Specifically, a moderate intensity monofilament will be applied once per second for approximately 15-20 seconds to the most painful knee during multiple scanning runs, followed by an equivalent time period of no stimulation. We expect to observe increased pain-evoked activation among African Americans in the anterior cingulate, dorsolateral prefrontal cortex, and periaqueductal gray, and reduce activation following the intervention.

For structural MRI, we will acquire a high-resolution anatomical MRI, and regional gray matter volume will be assessed using voxel based morphometry, and post-processing techniques that provide measurement of regional brain structural volumes. We expect to observe lower gray matter volume among African Americans in the insula, anterior cingulate cortex, hippocampus and inferior temporal cortex. Also, high angular resolution diffusion imaging will be used to examine white matter tracts connecting brain regions. We may also use diffusion imaging to examine white matter tracts as a measure of structural connectivity.

MRI scanning will be carried out at the UF CTSI Human Imaging Core facility located in McKnight Brain Institute and at a comparable facility at UAB. A state-of-the-art 3.0T whole-body clinical MRI system will be used. The imaging protocol is designed to allow for acquisition of all scans in one imaging session lasting approximately 60 minutes, which is typically well tolerated by research subjects. We expect that most participants will be able to complete the entire imaging protocol; however, some individuals may become fatigued before completing all segments. Therefore, the most critical measures will be collected early in the protocol. Ear plugs will be placed in the subject's ears to reduce the scanner noises. A headphone will be placed over the subject's ears for operator-subject intercom purpose and further reduction of the scanner noise. The subject will lie on the patient table in supine position, with the head being placed in the head coil.

D2.2 Intervention Description

Overview: The intervention is planned to be delivered over 5 consecutive days, with each intervention session lasting 45-60 minutes. All participants will undergo the assigned BAT (standard vs. focused) and tDCS (real vs. sham) treatments in combination. Thus, individuals will be practicing the BAT while tDCS (real or sham) is being delivered. Upon arrival, participants will be seated comfortably and instrumented for tDCS (see below). Then tDCS stimulation will commence and the BAT instructions will be provided.

Transcranial Direct Current Stimulation (tDCS): *M1-SO Montage*. A Soterix 1x1 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 SO (Fp1 or Fp2) ipsilateral to the index knee. Participants will receive stimulation in each of five visits over one week, while performing real versus sham BAT. *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. 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 Co-I Woods (77). Physiological Recording: During stimulation sessions participants may be asked to wear a special wristband that will be used to record physiological information such as pulse. Quality Control: In some participants, we may take a brief set of pictures of the participant's head after the electrodes are placed to make sure that the electrodes are in the correct location. These photos will be used to create a 3D model of the participant's head that will give us accurate information about where the electrodes were placed.

Breathing and Attention Training (BAT): We will use a well-validated mindfulness-based mental training regimen to teach participants to independently practice mindfulness meditation (5, 24, 27, 49, 67, 68). We will describe this to participants as Focused-Breathing and Attention Training (F-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. Each of the five sessions will last approximately 20 minutes, during which 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 the fourth and fifth sessions, participants will receive minimal instructions, and will meditate during an audio recording of the MRI sounds (5, 49). Standard-Breathing and Attention Training (S-BAT): The main purpose of the S-BAT intervention is to incorporate most of the general aspects of the BAT intervention but *without the specific instructions related to mindfully attending to the breath in a non-evaluative manner* (5, 78). This regimen is designed so that the primary difference between the focused and standard BAT is the F-BAT group's explicit mindfulness-based instructions (e.g., mindful attention to the breath). Thus, the S-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 (5, 78). 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 (5, 78). 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 session 3. In sessions four and five, subjects will receive minimal instruction and will "meditate" during an audio recording of the MRI sounds.

We recognize that scheduling five daily visits is a challenge, and we expect missed visits for some participants. If participants miss only one of five visits, that will not be considered a protocol deviation; however, if they miss two or more visits, this will be reported as a minor deviation.

Additional Post-Treatment Measures: We will assess the following measures post-treatment. 1) Side Effects: Participants will complete a brief questionnaire assessing side effects of treatment, including side effects that can occur with tDCS (e.g. tingling, itching, headache, fatigue) or mindfulness (breathing changes, dizziness, sleep changes, anxiety). And participants will be asked whether they believe they received real or sham tDCS. 2) Treatment Satisfaction/Helpfulness: Participants will provide a rating of overall satisfaction with treatment, and a rating of how helpful they found the treatment for reducing their pain. 3) Three-Month Follow-Up: Each month for three months post-intervention, participants will complete a follow-up questionnaire, including the NRS assessing average pain over the past 24 hours, as well as ratings of pain interference and mood. We will also administer the PSS and the PCS at these follow-up time points. At the final follow-up assessment, we will ask participants to report on their global impression of treatment helpfulness and to indicate

whether and how often they continue to use their BAT skills. 4) Debriefing: After the final follow-up assessment, one of the research team members will telephone the participant to explain the purpose of the study. At this time, we will not be able to reveal which tDCS group they were in, as the investigators will remain blind to this. In addition, we will not reveal which BAT condition they received, because if participants communicate such information to others who are in the study, this could bias study results. Interested participants will be directed to online resources to learn more about mindfulness.

D3. Data Analysis: Sample Size and Statistical Power**:** In this study, we are proposing to randomize 360 individuals to four groups defined by a 2X2 factorial design, and we expect to have 320 completers. Table 4 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 our previous studies (4, 5). We plan to conduct six primary hypothesis tests (Sham vs Real BAT and Sham vs. Real tDCS for three primary outcomes) with the use of F-test at a corrected α=0.0083 significance level. Even with this conservative approach, we have 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.

Table 4: Effect Sizes Observed for tDCS and MMT in our Previous Work

		Power for Different Sample Sizes		
Outcome	Cohen's D	N = 300	N = 320	N = 340
tDCS (from Ahn, et al)				
CPM	0.34	0.61	0.65	0.68
Pain Rating	0.44	0.88	0.90	0.92
MMT (from Zeidan, et al)				
Heat Pain	0.51	0.97	0.98	0.99
rCBF	0.82	0.99	0.99	0.99

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.
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:

$$E(Y) = \beta_0 + \beta_1 BaselineScore + \beta_2 Covariates + \beta_3 BAT + \beta_4 tDC + \beta_5 AA +$$

$$B_6 BAT*tDCS + \beta_7 BAT*AA + \beta_8 tDCS*AA + \beta_9 BAT*tDCS*AA,$$

where BAT and tDCS are dummy variables for interventions, AA is the dummy variable for African Americans. Linear contrast will be employed to test the main effect 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 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 AA 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 race and intervention. Point estimates and 95% confidence intervals will be obtained for the 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.
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 AAs vs. NHWs.

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 and 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 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. Possible Discomforts and Risks:

Potential risks are minimal and relate primarily to short-term discomfort of the sensory testing procedures delivering cold and mechanical pressure. The risks from brain imaging procedures are thought to be minimal in appropriately screened participants. Questionnaires include specific questions about how a participant feels and ask the participant to think about life experiences. Reading or answering these questions may cause some participants embarrassment or discomfort.

Potential Risks

Mechanical pressure: pressure is delivered by a hand-held algometer (spring-controlled device delivering calibrated pressure via a flat 10mm diameter rubber tip). Pressure is delivered at an approximate rate of 30 kPa/sec. Participants will be instructed to signal by pressing a button when the pressure sensation first becomes painful at which time the researcher removes the algometer. There is little opportunity for bruising or other transient trauma from this procedure. Also, mechanical punctate stimuli will be delivered using a nylon monofilament. Risk associated with this procedure is minimal.

Cold Stimulation: Cold is delivered by having subjects immerse their hand in cold water. This can produce temporary discomfort, which subsides with withdrawal of the hand. No other risks are known. Participants may stop at any time.

Magnetic resonance imaging (MRI): MRI is a procedure that allows doctors to look inside the body by using a scanner that sends out a strong magnetic field and radio waves. This procedure is used routinely for medical care and is very safe for most people, but participants will be monitored during the entire MRI scan in case any problems occur. The risks of MRI are:

- The MRI scanner contains a very strong magnet. Therefore, participants may not be able to have the MRI if they have any type of metal implanted in their body, for example, any pacing device (such as a heart pacer), any metal in their eyes, or certain types of heart valves or brain aneurysm clips. A MRI technologist will question participants about any contraindications before they enter the scanner.
- There is not much room inside the MRI scanner. Participants may be uncomfortable if they do not like to be in close spaces ("claustrophobia"). During the procedure, participants will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, participants can tell them to stop the scan.
- The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of participants. Participants will be given earplugs to reduce this risk, and headphones for added protection.
- If an obvious abnormality is discovered during the participant's MRI scan, they will be informed about it by the research team, and will be provided with a copy of the MRI scan and we will encourage them to see their primary care physician. MRI will only be done for research purposes in this study.
- Participants will be monitored very carefully while in the scanner, and repeatedly checked to ensure comfort.

Transcranial direct current stimulation: Transcranial direct current stimulation is considered safe but a small number of people do experience some side effects. The most common side effects are itching and tingling or mild discomfort at the area of stimulation, and headache. Other possible side effects include dizziness and nausea. Whenever an electrical stimulation is applied to the body, it could possibly cause a seizure or abnormal heartbeat, but this has never occurred with the transcranial direct current stimulation parameters used in this study.

Breathing and Attention Training (BAT): The brief BAT intervention in this study carries minimal risks. Some participants may become uncomfortable while focusing on their breathing and letting go of thoughts and feelings. We will instruct participants to alert the experimenter if they experience discomfort during the treatment.

Survey questionnaires: Potential risk involves participant feelings of discomfort or unease when reading or responding to survey questions that are personal. Throughout each questionnaire, participants are reminded that participation is completely voluntary, they can refuse to answer any question or can stop at any time.

Adequacy of Protection against Risks.

Our inclusion and exclusion criteria are designed to minimize risks to participants.

A total of 360 (180 African American, 180 non-Hispanic whites) adults with symptomatic knee osteoarthritis (OA), between 45 and 95 years of age will be enrolled. Half of these participants will be enrolled at UF and the other half at UAB. Similar to our previous work, the inclusion criteria for participants are:

1) Unilateral or bilateral symptomatic knee OA based on American College of Rheumatology Clinical criteria (1).
2) Age 45 – 95; this age range was chosen because the prevalence of knee OA is substantially lower before age 45, and participants over 95 years are increasingly likely to meet one or more exclusion criteria. This relatively broad age range will allow us to examine potential age-related influences on responses to the proposed interventions.
3) Participant reports primary ethnic/race group as either African American or non-Hispanic white.

Participants will be excluded if they have any concurrent medical conditions that could confound interpretation of outcome measures, pose a safety risk for any of the assessment or intervention procedures, or preclude successful completion of the protocol. Specific exclusion criteria are:

- Actively symptomatic systemic rheumatic disease/condition (e.g. rheumatoid arthritis, systemic lupus erythematosus), or fibromyalgia that results in pain outside the knee that is equal to or worse than the participant's knee pain.
- A history of clinically significant surgery to the index knee.
- Daily use of opioids. We will exclude patients using opioids daily as both continued use and temporary withdrawal from these medications this could affect pain perception and response to interventions. Other medications being used will be recorded and controlled in statistical analyses as needed.
- Use of some centrally acting sodium channel blockers and NMDA receptor antagonists, because some of these medications can block tDCS effects. Other medications can potentially influence response to tDCS (e.g. SSRIs, beta-blockers); therefore, consistent with recent recommendations (2), we will assess use of these medications and include them as covariates in our statistical models.
- Uncontrolled hypertension (i.e. SBP/DBP of $\geq$ 150/95) or unstable or activity limiting cardiovascular or peripheral arterial disease. These exclusions are in place primarily for safety reasons, because the cold pressor task represents a cardiovascular challenge. However, uncontrolled hypertension can also affect pain perception, which is another reason for excluding these individuals.
- Neurological disease (e.g. Parkinson's, multiple sclerosis, epilepsy) or evidence of previous brain injury, including stroke and traumatic brain injury.
- Serious psychiatric disorder requiring hospitalization within the past 12 months or characterized by active suicidal ideation.
- Current substance use disorder or history of hospitalization for treatment of substance use disorder.
- Diminished cognitive function that would interfere with understanding of study procedures.
- Chronic pain is more severe at any other body site other than the knee

Protection against Risk.

*Protection against risk to confidentiality***.** Information collected as part of this research protocol will be maintained in locked filing cabinets and password protected databases accessible only to study personnel. All study staff will be trained in handling human subject information to maintain privacy and confidentiality. Procedures for allowing access to investigators to use this information for research will be under the authority of the PI and will follow HIPAA compliant guidelines for the release of PHI.

No results will ever be reported in a personally identifiable manner. All research data will be entered directly into a web-based survey that is maintained by the University of Florida CTSI (REDCap). The data will be stored on secure servers at the University of Florida and will be accessible only to trained study personnel. A Certificate of Confidentiality will be obtained from the NIH for this project.

Protections of risks related to study questionnaires. To minimize any risks related to emotional responses to questionnaires, persons will be informed about the types of questions included in the surveys, which are similar to the types of questions persons might be asked by their doctor in a clinical setting. They will be informed that they can refuse to answer any questions if they so choose.

Protection of risks related to tDCS. To minimize risk associated with tDCS, participants will be monitored throughout stimulation sessions and asked to report any discomfort. If scalp sensation is uncomfortable, stimulation will be stopped. In the event of a headache, stimulation will be stopped. All tDCS sessions will be administered and continually supervise by a trained experimenter. The above symptoms have only been reported when participants are actively being stimulated. tDCS has

not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by tDCS in human participants in the literature. However, this may not be true for epilepsy patients, whose seizure threshold rates are likely abnormal. Prior history of neurological disorders is an exclusionary criterion for our study and thus no participants will have a history of seizure.

Protection against risks related to BAT. The BAT intervention carries minimal risk, however some individuals may become uncomfortable attending to their breathing and their thoughts and feelings. Participants will be encouraged to alert the experimenter if they experience discomfort, and the intervention will be halted.

Protection against risks associated with neuroimaging. MRI is widely regarded as a safe, noninvasive procedure for visualization of brain tissue in both adults and children. Prior to study participation, all participants will be informed of the MRI procedure during the informed consent/assent process. The proposed study will be performed on an FDA approved Siemens 3 Tesla scanner located at the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) research facility at UF. There are no known long-term effects of MRI procedures on the body. The FDA Information Sheets, Food and Drug Administration, October 1995, p. 79, lists as a non-significant risk device, “Magnetic Resonance Imaging (MRI) Devices within FDA-specified parameters.” This study satisfies those parameters. The 3.0 tesla MR scanners meets FDA parameters for field strength, gradient switching, and RF power deposition for all FDA-approved acquisition schemes including echo-planar imaging. Both our study staff and trained MRI staff will check for exclusion criteria. The main MRI-related risks include: (a) sensitivity to the loudness of the MRI machine - all subjects will be given and must wear ear plugs; a squeeze-ball and microphone will be provided so that they may stop the testing if they become uncomfortable or anxious at any time; (b) claustrophobia - subjects will have the opportunity to practice in a simulator and to become as familiar and comfortable as possible before commencing the experiment. In addition, they will be given the opportunity to examine the scanner before the tasks starts. The study will be ended early if the space is a problem for them; no medications (e.g., benzodiazepines or tranquilizers) will be offered to them; (c) lightheadedness when sitting up after lying in the MRI machine - this feeling sometimes occurs but has always gone away in a few minutes. Participants will thus be assisted in getting up to make sure they do not fall; In sum, the MRI neuroimaging procedures pose no radiological or medical risk, given that participants with metal implants susceptible to magnetic heating will be excluded based on standard scanner policies. A small number of people may become anxious in the small space of the scanner. These individuals will have the opportunity to terminate the scan session. Furthermore, all recruits will be screened for phobias prior to enrollment.

Incidental Findings: The technologist completing the MRI scan will review each structural scan for any gross abnormalities. If any suspected abnormality is detected, the technologist will have the scan reviewed by a physician in order to determine whether the participant should be informed. If the physician determines that the abnormality should be followed up, the study team will notify the participant that a potential abnormality was detected on their brain scan and encourage them to follow up with their health care provider.

In summary, risks are low and appropriate safeguards are planned and in place to handle risks in a timely and appropriate manner.

8. Possible Benefits:

There is potential for direct benefit to the participants, as the interventions, either alone or in combination may improve their knee OA symptoms. In addition, the findings from the study could lead to substantial societal benefit in the form of new interventions for knee OA pain. Knee OA is the most common form of OA and produces substantial disability and reduced quality of life. Minority groups, especially African Americans, appear to be disproportionately impacted. Given this prevalence and enormous societal impact, this study aims to target factors contributing to ethnic

group difference in pain and disability associated with knee OA. This information has the potential to improve treatment of knee OA in the future and to reduce ethnic/racial disparities in OA pain.

Importance of the Knowledge to Be Gained

The information obtained will provide novel and important information regarding the benefits of two interventions that target the biological and psychosocial factors contributing to ethnic differences in OA-related pain and disability. This will provide the foundation for more informed intervention strategies in the future, which may reduce racial and ethnic disparities in OA pain and disability.

Inclusion of Women and Minorities

Ethnic differences are a major aspect of the proposed research; therefore, both African Americans and non-Hispanic whites will be equally represented, each comprising half of the total sample. Other ethnic groups will not be included in this study, given the focus of the research; however, our goal is to extend the work to other minority groups in the future. Both sexes will be included, and we anticipate enrolling more women (60-65%) than men (35-40%), but recruitment will be monitored to ensure equal sex ratios in each ethnic group.

Data and Safety Monitoring Plan

While this is not an efficacy trial, this does meet the definition of a clinical trial. The trial will be registered in ClinicalTrials.gov. Therefore, we will establish a Data Safety and Monitoring Board (DSMB) comprised of experts who are external to the project to monitor the project. The DSMB will perform the following functions:

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Report to NIA on the safety and progress of the trial;
- Make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

Progress reports summarizing study enrollment, adverse events, data quality, and intervention fidelity will be provided to the NIA and DSMB at least annually. The DSMB will review these reports and hold a teleconference with the study investigators to review the outcomes. The DSMB will provide the NIA and study team a written report with recommendations after each teleconference. Any subsequent recommendations regarding protocol changes will be addressed by the study team. In addition to reporting to the DSMB and NIA, all adverse events will be reported to the IRBs at each institution for their review. Also, the investigators will monitor reported adverse events on an ongoing basis and consider protocol modifications to minimize risks to the study subjects.

9. Conflict of Interest

None

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