Cover Letter

Title of the study: Contribution of Pain Catastrophizing to Race Group Differences in Pain and Pain-Related Brain Responses in Older Adults With Knee Osteoarthritis (OA)

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Protocol

1. Project Title: Contribution of Pain Catastrophizing to Race Group Differences in Pain and Pain-Related Brain Responses in Older Adults with Knee OA. [Study of Pain Catastrophizing] (SPAC)

2. Investigator(s): Ellen L. Terry, Ph.D. (PI)
Roger B. Fillingim (Primary Mentor)

3. Abstract:

Previous research demonstrates that non-Hispanic blacks (NHB) with osteoarthritis (OA) experience more frequent and severe clinical pain, greater disability and show a quantitative sensory testing (QST) profile suggesting impaired pain inhibition and enhanced generalized pain facilitation compared to their non-Hispanic white (NHW) counterparts. In addition, previous findings demonstrated higher pain catastrophizing (a tendency to negatively evaluate one's ability to cope with pain and to respond to anticipated or actual pain in a heightened negative cognitive and emotional manner) among NHBs compared to NHWs. While multiple factors inevitably contribute, race group differences in cognitive and affective processes (e.g. catastrophizing), represent potentially important determinants of greater clinical pain among NHBs, perhaps by altering central pain processing. Despite its pervasive negative effects, no neuroimaging study to date has experimentally manipulated pain catastrophizing and measured cerebral activity during experimentally-induced pain to determine the neural mechanisms whereby catastrophizing impacts pain responses. Moreover, the extent to which the influence of pain catastrophizing on these central pathways contributes to ethnic group differences in the experience of pain remains unexplored. To address this, the proposed study will characterize the impact of an anti-catastrophizing cognitive-behavioral intervention on pain-related neural processes and pain among NHBs and NHWs with knee OA. NHB and NHW participants with symptomatic knee OA will be randomly assigned to a brief pain catastrophizing reduction cognitive-behavioral intervention or a control group that will receive pain education. Testing will occur over three days. Participants will complete neuroimaging, including assessment of pain-evoked cerebral responses and experimental pain testing (i.e., QST) prior to and after the intervention session. Standardized quantitative sensory testing approaches will be used to assess experimental pain sensitivity, as well as their State Pain Catastrophizing Scale (S-PCS). We hypothesize that baseline levels of catastrophizing will be higher among NHB subjects and will predict increased pain sensitivity and greater pain-related brain responses among NHB participants. Moreover, we anticipate that the anti-catastrophizing reduction intervention will produce greater reductions in reported pain and in pain-related brain activity among NHB versus NHW participants. Findings from this proposed study will provide novel information regarding the neural mechanisms whereby pain catastrophizing modulates pain and the extent to which these neural processes contribute to ethnic group differences in pain responses among NHBs and NHWs with knee OA. This project will yield important preliminary data for a future grant application seeking support for a larger scale clinical intervention study targeting pain catastrophizing to reduce disparities in pain among older adults.

4. Background:

Clinical osteoarthritis (OA) is the most commonly diagnosed disease with prevalence rates of approximately 27 million US adults and rates are projected to increase as the population age [26; 31], resulting in an annual economic cost of $128 billion [8]. The knee is the most commonly affected joint and accounts for the largest proportion of OA burden [54]. Data from a large

representative study revealed that non-Hispanic blacks (NHB) have higher odds of being diagnosed with radiographic (1.7 times) and clinical (1.5 times) knee OA than non-Hispanic whites (NHW) [14]. Furthermore, NHBs with knee OA have higher prevalence rates of radiographic and symptomatic knee OA and they experience substantially higher levels of knee OA-related chronic pain, functional limitations, and disability compared to their NHW counterparts [2; 22; 52]. In addition, NHBs with knee OA show deficits in pain modulation during experimental pain testing, such that they evince enhanced pain facilitation and impaired pain inhibition compared to NHWs [11]. This quantitative sensory testing profile likely contributes to greater experimental and clinical pain sensitivity and may be a phenotype of pain risk in NHBs. Together, these findings suggest that ethnic group differences in central pain processing represent a potentially important determinant of greater clinical pain among NHBs. While numerous factors likely contribute to ethnic differences in OA-related pain and other adverse outcomes [3; 19], interventions targeting psychosocial factors have been shown to be a promising avenue to reduce pain and reverse aberrant central pain processing in patients with chronic pain [27; 41], but less emphasis has been devoted to addressing ethnic differences in knee OA using interventions aimed at addressing psychosocial factors [1].

A robust psychosocial predictor of enhanced pain and pain-related outcomes is pain catastrophizing. Pain catastrophizing is a tendency to negatively appraise pain-related experiences, thereby feeling overwhelmed and having lower perceived ability to cope with and control pain, thus, resulting in an amplified pain experience and adverse pain-related outcomes (e.g., disability) [30; 43; 44]. Considerable evidence identifies pain catastrophizing as a consistent psychosocial variable that predicts poor pain and pain-related outcomes [34; 50] across multiple chronic pain conditions [18; 23; 33; 38; 45-47; 51], including in patients with knee OA [6; 28; 29]. Numerous studies have documented higher pain catastrophizing in healthy pain-free NHBs compared to NHWs during experimental pain tasks [35]. Similarly, investigations of race difference in pain catastrophizing in patients with knee OA and other chronic pain conditions, suggest NHBs report higher pain catastrophizing during both experimental and clinical pain, compared to NHWs [10; 16; 21; 39]. While the importance of intervening on pain catastrophizing has been established, research is needed to better understand its neural correlates in order to improve treatment efficacy [42].

Neuroimaging studies have associated pain catastrophizing with increased cerebral responses to pain in several pain-related brain regions (e.g., medial frontal cortex, anterior cingulate cortex [ACC], dorsolateral prefrontal cortex [dlPFC], insula, and primary somatosensory cortex [SI]) [9; 15; 18; 40], and with increased resting state connectivity between SI and insula [27]. A recent systematic review of brain changes associated with pain catastrophizing reveal there is some evidence for alterations in gray matter morphology and resting state functional connectivity in patients with chronic pain following reduction of pain catastrophizing [32]. Indeed, compelling evidence demonstrates that successful reduction of pain catastrophizing following cognitive behavioral therapy was significantly correlated with gray matter increase in several pain related brain regions (e.g., dlPFC, S1, ACC) [41]. Furthermore, reduction of pain catastrophizing with cognitive behavioral therapy resulted in the decoupling of resting state connectivity between SI and anterior/medial insula, brain regions not typically connected in a resting state [27]. However, Malfliet et al. [32] notes that these studies were observational, which limits conclusions about the causal effects of the treatment of pain catastrophizing and its influence on brain alterations. Therefore, no neuroimaging study to date has experimentally manipulated pain catastrophizing and measured cerebral activity during experimentally-induced pain to determine the neural mechanisms whereby catastrophizing impacts pain responses. Moreover, the extent to which the influence of pain catastrophizing on these central pathways contributes to ethnic group differences in the experience of pain remains unexplored.

The objective of the proposed research is to experimentally manipulate pain catastrophizing in order to investigate the neural mechanisms by which pain catastrophizing influences the

experience of pain among NHBs and NHWs with chronic pain associated with knee OA. Therefore, participants will be randomized to either a 30-minute, single-session catastrophizing reduction manipulation or a 30-minute, single-session pain education control group [48; 49].

5. Hypotheses and Specific Aims:

Specific Aim 1: To characterize the impact of an anti-catastrophizing manipulation on pain-related neural processes and pain among NHBs and NHWs with knee OA.

Hypothesis 1a. We hypothesize that the manipulation will produce greater reductions in experimental pain and clinical pain among NHBs than NHWs.

Hypothesis 1b. We hypothesize that the manipulation will produce greater reductions in pain-related brain responses among NHBs than NHWs.

6. Research Plan:

The proposed study will enroll 5 NHB and 5 NHW catastrophizing participants with symptomatic knee OA. The study will over-enroll 3 additional participants due to attrition over the three-day study period. Up to 180 additional participants may undergo screening procedures and will count toward screen failures. Potential participants will undergo a standardized telephone or in-person screening which will include the pain catastrophizing questionnaire, as well as screening questions that inquire about conditions that are listed under our inclusion and exclusion criteria to confirm initial eligibility. Participants will be informed that if they do participate in this study, we will keep the information the participant provide in addition to information provided to these questions as part of this research study. If the participant does not meet inclusion criteria or decides not to participate in the study, the participant will be informed that no additional information would be collected, but any information up to that point would be maintained. Thirty potential participants will be screened to determine initial eligibility. Patients will be excluded if they have concurrent medical or arthritic conditions that could confound symptomatic knee OA related outcome measures or coexisting disease that could preclude successful completion of the protocol including: systemic rheumatic disease/condition, including rheumatoid arthritis, systemic lupus erythematosus, gout, and fibromyalgia; a history of clinically significant surgery to the index knee (e.g. open reconstruction, knee replacement or major surgery on one or both knees); uncontrolled hypertension (> 150/95); loss of peripheral sensation in areas of the body that will be tested with QST; certain neurological diseases that could interfere with protocol completion such as s Parkinson's disease, multiple sclerosis, stroke with loss of sensory or motor function, or uncontrolled seizures; cardiovascular or peripheral arterial disease; serious psychiatric disorder requiring hospitalization within the past 12 months; diminished cognitive function that would interfere with completion of study procedures. Daily opioid use will also be an exclusion, as well as a Pain Catastrophizing Score of less than 10. Hospitalization within the preceding year for psychiatric illness, serious psychiatric disorder requiring hospitalization within the past 12 months or characterized by active suicidal ideation or diminished cognitive function that would interfere with completion of study procedures. Pregnancy will also be an exclusion. Also, contraindications to MRI scanning (e.g. presence of metal implants, claustrophobia) will be exclusion criteria. Any criteria for MRI Exclusion, such as the presence of non-removable metallic, magnetic material or devices such as pacemakers, aneurism clips, or claustrophobia, which could pose a risk for injury in the MRI scanner. The study will include questionnaires to assess pain, clinical symptoms, and pain catastrophizing. All questionnaires provided during this research study's timeline are shown in Table 2. Quantitative Sensory Testing (QST) will be performed at the Pain Clinical Research Unit (PainCRU), a fully equipped sensory testing lab within the UF Pain Research and Intervention Center of Excellence (PRICE) directed by Dr. Fillingim (mentor).

Brain imaging will be performed in the CTSI Human Imaging Core facility, in a 3.0 Tesla whole-body clinical MRI system (Simens Prisma) and a 32-channel head coil will be used (see study Timeline for procedure order).

The **Pain Catastrophizing Scale (PCS)** is a reliable and valid (coefficient alpha for total PCS = 0.87), 13-item scale that assesses catastrophic thinking associated with pain [44]. We will administer the PCS using traditional instructions (a measure of trait catastrophizing) and instructions to assess State Pain Catastrophizing Scale (S-PCS) ("Thinking back to your experience during the laboratory pain testing").

Table 2. Questionnaires administered by visit day

Day 1	Day 2	Day 3
Health History	Positive and Negative Affect Scale (PANAS)	Positive and Negative Affect Scale (PANAS)
Pain History	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	Treatment Expectation Questionnaire
REALM-R	Graded Chronic Pain Scale (GCPS)	Manipulation Check Questionnaire
Physical Exam Form	State Pain Catastrophizing Scale (S-PCS)	Coping Strategies Questionnaire-Revised (CSQ-R)
MRI Screening Form		State Pain Catastrophizing Scale (S-PCS)
Pain Catastrophizing Scale (PCS)		

Note: All questionnaires will be administered after written documentation of consent. S-PCS questionnaires will be administered after each pain testing task.

Clinical Pain. The **Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)** [5] is a reliable (Cronbach's alpha ≥ 0.80) and well-validated measure of lower extremity pain and function in persons with OA. The **Graded Chronic Pain Scale (GCPS)** evaluates global pain severity and pain-related interference over the past 6 months. It yields a "Characteristic Pain Intensity" and an overall "Disability" score [53]. The **Rapid Estimate of Adult Literacy in Medicine-revised (REALM-R).** A brief test to measure the participant's ability to read common medical words, in order to determine whether the participant may need assistance with completing questionnaires.

Quantitative Sensory Testing session (QST). Quantitative Sensory Testing Session. Using well-established procedures from our laboratory, all participants underwent assessment of responses to pressure, and mechanical pain in a laboratory session lasting 30-60 minutes, as described previously [16; 50]. ***Pressure Pain Thresholds (PPT):*** was assessed at the medial and lateral joint lines of the index knee, and at the ipsilateral quadriceps, trapezius muscle and lateral epicondyle. ***Punctate Mechanical Pain:*** assessed at the patella of the index knee and the dorsal aspect of the ipsilateral hand using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300g of pressure. As in our previous studies [16; 50], participants were provide a pain rating following a single contact of the monofilament, after which they provided another pain rating following a series of 10 contacts at a rate of one contact per second. The difference between pain ratings for the single versus multiple contacts reflects temporal summation of mechanical pain.

Neuroimaging Protocol. A high-resolution, 3D structural scan will be conducted using a T1-weighted MP-RAGE sequence for use in pre-processing all functional data which will be conducted between stimulus-evoked scans (Table 1). Two **resting state scans** will be acquired using BOLD-fMRI and pCASL in order to examine functional connectivity. Participants will be asked to close their eyes during resting state scans, but to maintain alertness during the scans. Any difficulty staying awake was assessed immediately following the resting-state scan. **Stimulus-Evoked fMRI and pCASL:** These procedure will be conducted to assess changes in regional brain activity to painful mechanical stimuli applied to the most painful knee of OA patients. Specifically, a monofilament that was individually calibrated to produce a moderate pain intensity rating of ≤ 50 out of 100 will be applied once per second for a total of five twenty-four second blocks to the index knee, followed by an equivalent time period of blunt stimulation (randomized order) with thirty-six second blocks

Table 1. MRI Sequences

Run	Paradigm	Min
-	Positioning	9.5
1	Resting fMRI BOLD Scan	8
2	Resting pCASL Scan	5
3	Mechanical Pain fMRI BOLD Scan	10
4	Anatomical Scan: T1 Weighted Image (3D)	4.5
5	Mechanical Pain pCASL Scan	10
6	Resting DWI HARDI Scan	7.5
7	FLAIR 3D (OPTIONAL Time Permitting)	5.5
	Total Time	60

of rest between each mechanical stimuli. One overall verbal pain rating (on the 0-100 scale) will be obtained following all stimuli. Data acquisition of all scans will occur in two 50.5-minutes imaging session, with 9.5 minutes for set up, resulting in a total 60-minute session.

Randomization and General Procedures. Individuals will be randomized to one of two groups (stratified by sex): 1) a 30-minute, single-session cognitive-behavioral intervention designed to reduce pain catastrophizing or 2) a control condition that receives pain education. Testing will occur on two days (Figure 1). On Day 1, participants will attend a laboratory session whereby informed consent will be reviewed; health, pain, and demographic history will be obtained and physical examination will be performed to identify the most symptomatic knee. Female participants of childbearing potential will complete a one-time pregnancy test at the beginning of the session on day one. Trait pain catastrophizing will be assessed prior to pain testing. Day 1 session is expected to last up to 1.5 hours. On Day 2, participants will undergo neuroimaging acquisition followed by assessment of State Pain Catastrophizing Scale (S-PCS) in response to the pain-evoked cerebral responses (see **neuroimaging protocol** above). Then, participants will complete QST assessment of responses to pressure (i.e., pressure pain threshold), and punctate mechanical stimuli (i.e., temporal summation of mechanical pain) in a laboratory session lasting 30-60 minutes. State Pain Catastrophizing Scale (S-PCS) will be assessed immediately after each pain induction procedure. There will be a 30-minute rest period between the neuroimaging and QST session. Day 2 session is expected to last 2.5 to 3 hours. On Day 3, each participant will receive either the cognitive-behavioral intervention or the pain education (control condition), followed by post-tests that will be identical to the pre-tests given on Day 2, except that participants in the pain catastrophizing reduction group will be told to use the coping strategies they learned. Once all testing is over, participants will be debriefed and provided with an honorarium. Day 3 testing session is expected to last 3 to 3.5 hours. Audio recording will be conducted at the end of the study in order to obtain feedback on what intervention techniques participants used and whether they noticed any difference during Day 3 testing. We will audio record responses to the following questions: 1) during this last testing, please tell us what you were able to do; 2) describe how you applied your techniques; 3) did you notice any difference in your reactions to the stimulations; and 4) what did you notice? Further, participants will be asked to rate on a scale from 0-10 how well they were able to use the strategies and how effective they felt the strategies were. These recording will be reviewed by the study team to assess the quality of our treatment visits. These recording will not be released and will only be accessible by study investigators. At the end of the study, the recordings will be transcribed and the audio recordings will be destroyed. State Pain Catastrophizing Scale (S-PCS) will be used as a manipulation check to verify that catastrophizing was effectively. **Pain Catastrophizing Reduction Group:** The cognitive-behavioral intervention will comprise three components: 1) general education about pain (e.g., pain pathways) and a rationale for the intervention (e.g., gate control theory); 2) impact of positive and negative pain-related thoughts on neural process of pain; and 3) a guided imaginal pain exposure exercise. We and others have successfully applied these and similar approaches to reducing pain catastrophizing [12; 13; 48; 49] (see manual for details). **Pain Education Group:** This group will receive general information about the neurobiology of pain and knee OA. At no time will they be taught about pain modulation or the interface of thoughts, feelings, and pain [48; 49].

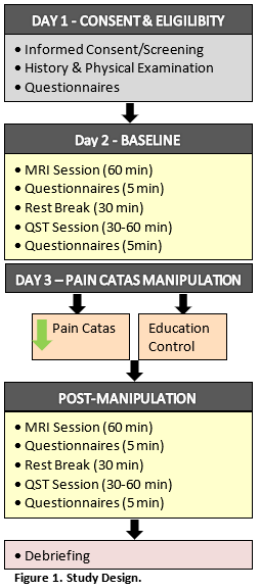

Figure 1. Study Design. Catas=Catastrophizing; MRI=magnetic resonance imaging; QST=quantitative sensory testing.

FMRI Analyses. Resting State BOLD: We will perform functional connectivity analysis. Briefly, the BOLD images will be pre-processed using MATLAB Statistical Parametric Mapping software (SPM12) scripts [17]. The images will be slice time corrected, realigned, and resliced into 2mm x 2mm x 2mm voxel sized images and spatially normalized to an EPI template. Movement artifacts

are processed using the paradigm set forth in [7; 37]. Movement effects are first regressed from the BOLD signal. If movement is greater than 0.5mm, bad volumes will be identified and replaced with interpolated values (using nearest neighbor interpolation). Effects attributed to cerebrospinal fluid and white matter will then be regressed out from the BOLD signal. The whole data set is temporally smoothed using a band-pass butterworth filter (freq=[0.01 0.08]) and spatially smoothed using a Gaussian model (6 mm kernel), and interpolated volumes removed. Functional connectivity (r to z transformed correlations coefficients) between regions of interest (ROIs) associated with pain catastrophizing [27] (dorsolateral prefrontal cortex and anterior cingulate cortex, and insula and SI) will be assessed using the CONN Toolbox [55]. **Evoked-Pain Scans:** mechanical stimuli will be applied once per second for 10 twenty-four second periods with 36 seconds of rest periods following each stimulus series for the scan duration (as in [20]). Preprocessing steps will include: motion correction, residual motion effect removal, denoising, co-registration, spatial smoothing, and normalization. Based on the existing literature on pain-evoked stimuli, we will examine the following ROIs [4; 36]: anterior cingulate cortex, dorsolateral prefrontal cortex, and the periaqueductal gray [PAG]. These ROIs will be selected with the Wake Forest University pick atlas, which uses the Talairach Daemon database [25].

Data Analysis. Procedures will be put in place to ensure data integrity and the protection of subject identification. Data will be inspected for distributional form, missing values, and implausible values. We will compare data on study completers and those lost to follow-up to investigate potential biases. The assumption of normality will be checked using histograms and normal probability plots. The assumptions of regression and mediation models will be checked using residual plots and plots of influence statistics. All statistical analyses will be conducted with statistical software SAS version 9.4 (Cary, N.C.) and R version 3.2.2 (The R Foundation for Statistical Computing). All hypothesis testing conducted to address the primary aim (comparing ethnic groups on pain-related brain function, clinical pain, and pain sensitivity measures) will be two-sided with a Bonferroni corrected level of significance of .004 (.05 divided by 12 tests). Hypothesis testing using ANCOVA models will also be two-sided with a Bonferroni corrected level of significance of .004. We will control for SES and discrimination in all analyses.

We will use separate ANCOVA models to investigate the effect of the manipulation (the independent variable) on pain-related neural processes and pain measures. The measures at baseline are the covariates while the measures post-manipulation are the dependent variables. We will again use separate ANCOVA models which will include an ethnic group variable and an manipulation-ethnic group interaction term to test the hypothesis that the manipulation will produce differentiated pain-related brain responses due to ethnicity.

7. Possible Discomforts and Risks:

Potential Risks:

While generally safe, the experimental pain procedures confer some limited risks. One risk common to all procedures is that the participant will experience pain or discomfort. Specific risks of each procedure are discussed below.

Pressure Pain Procedure: There is a slight chance that a bruise may form as a result of the pressure pain procedure. Also, some patients may experience after-sensations after application of pressure stimuli to their symptomatic knee, though this is expected to be brief in duration. Also, this risk is diminished by applying brief stimuli well below the participant's tolerance level.

Magnetic Resonance Imaging (MRI): MRI scanning does not expose subjects to any physical risks by itself. All subjects will be carefully screened for the presence of magnetic material or devices, like pacemakers, etc. that could pose a risk for injury in the MRI scanner. They will

only be allowed into the magnet if magnetic or electronic items can be removed prior to scanning. Some subjects who experience fear of enclosed spaces (i.e. claustrophobia) may not be able to undergo brain MRI scanning. Participants will also be carefully screened for claustrophobia before conducting fMRI scanning.

Protections Against Risk:

The experimental pain procedures described in this application are widely used and safe procedures. While they produce pain, risk to the subject is minimal, because: 1) the pain is transient in nature, and generally subsides immediately after the procedure; 2) subjects are instructed that they may stop any procedure at any time with no adverse consequences; and 3) the level of pain experienced by subjects is below their tolerance level. Also, risks will be minimized by adhering to our exclusion criteria. Specific protections included in each procedure are discussed below.

Pressure Pain Procedure: The risks of bruising and lingering pain will be diminished by applying brief stimuli well below the participant's tolerance level.

MRI Procedures: The primary risk of MRI involves scanning in the presence of magnetic implants or material attached to the participant. Also, claustrophobic responses can be another risk. These risks will be minimized through careful screening of participants, both over the phone and again in-person prior to the imaging procedure. Also, participants will be informed that they can discontinue the procedure at any time should they become uncomfortable. Our team will observe the following procedures to reduce risks associated with the MRI protocol.

MRI Pre-Scan Procedures

All subjects in our study will be screened for standard MRI contraindications, including but not limited to:

- The presence non-removable ferrous metal objects
- Aneurysm clips
- Pacemakers
- Other contraindications such as defibrillators, etc.
- Claustrophobia or other subjective discomfort in the scanning environment

Subject Positioning:

Proper patient positioning is a key aspect for a successful and comfortable MRI exam. All subjects will be positioned in the same manner for MRI scanning. As a key component of our MRI scanning quality control to insure consistent and safe imaging of the brain, the following patient positioning procedure has been established:

1. Place clean sheet on scanner table and coil cradle.
2. Remove all upper body clothing with metallic trim, such as zippers, buttons or embroideries that may cause artifacts in the MRI images.
3. Provide each patient with ear protection (ear plugs and a headset).
4. Position the patient so the head and neck are relaxed, but without rotation in either plane. The patient should also be well supported in the head coil to maximize comfort and minimize movement.
5. Pillows are placed under the legs to help to decrease strain on the knees as well as assisting in the stabilization of motion in the lower body.
6. Once the patient has been positioned, place sponges along the sides of head for stabilizing support and reduction of motion.

7. Align the centering crosshairs on the patient's nasion (directly between the eyebrows) at every scanning session.
8. Center the head coil over the patients' head, making sure that the patient is high enough in the coil to ensure there is no drop off at the inferior aspect of the brain.
9. The subject is given an alarm ball, and instructed to squeeze the alarm ball in case he/she wants to have the scanning discontinued or needs to initiate communication with the operator of the scanner.
10. The subject is reminded to hold as still as possible and is then advanced to the iso-center of the scanning bore.

These procedures ensure maximum patient safety and comfort while allowing successful and reliable imaging of the brain.

8. Possible Benefits:

These risks are small relative to the potential benefits to be realized from conducting this research. While participants will not directly benefit from this research, it is hoped that the information to be gained will benefit society by providing new information regarding the neural factors by which pain catastrophizing influence pain and the underlying ethnic group differences in pain and disability.

9. DSMP (Data and Safety Monitoring Plan):

The current study is not a Phase III clinical trial nor does not involve multiple field sites. However, the current study involves greater than minimal risk, therefore, a formal data safety and monitoring board will not be required. In order to ensure data integrity and safety of human subjects, all adverse events will be reported to both the IRBs and the General Clinical Research Center for their external review. Any subsequent recommendations regarding protocol changes will be implemented. In addition, the PI (Ellen L. Terry) will review the reported adverse events every three months and will conduct interim data analyses to minimize the risk to the study subjects.

10. Conflict of Interest:

The PI (Ellen L. Terry) has no conflict of interest to disclose.

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