UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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1. PROJECT TITLE

Mechanisms of Affective Touch in Chronic Pain

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

Altman Clinical and Translational Research Institute (ACTRI)
UCSD Center for Functional MRI (CfMRI)

4. ESTIMATED DURATION OF THE STUDY

The proposed project will be ongoing for up to three years.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The proposed study will see whether light and deep types of touch, common in massage therapies, reduce pain as much (or more) than other types of touch. We will also study whether these types of touch have different effects in people with chronic pain. Finally, we will examine psychological factors that might explain differences in touch perception in individuals with chronic pain. This research will improve our understanding of how massage therapy can benefit pain and health, and how this might differ in people who suffer from chronic pain.

6. SPECIFIC AIMS

Light stroking and deep pressure touch are engaged by many complementary health practices, most notably massage therapy. Massage therapy uses touch in a therapeutic context to achieve significant reductions in stress, pain, and depression [1]. There is little understanding, however, of the mechanisms by which specific touch components- such as light stroking and deep pressure- exert affective and analgesic benefits. The pleasantness of light stroking touch has been linked to the activation of C low-threshold mechanoreceptor (C-LTMR) fibers, unmyelinated sensory fibers that respond to slow gentle stroking of the skin and project to opioidergic brain regions including the insula and cingulate cortex. How C-LTMR stimulation gives rise to pleasant sensation is unknown, though studies of monkeys (e.g. [2]) and preliminary data from humans [3] suggest that opioids play a role. The affective sensory pathways of deep pressure touch, in contrast, are less studied. Numerous clinical studies have found that deep pressure touch is calming and is superior to light touch in massage therapy [4, 5]. In addition, analgesic benefits of both light touch and deep pressure have been demonstrated in the laboratory [6, 7]. However, there is a significant gap in our knowledge of how these pathways differ in individuals with chronic pain, and whether pleasant touch has the same level of analgesic effect. In our previous work, chronic pain patients showed reduced perception of C-LTMR-optimal touch: in striking contrast to healthy volunteers, pain patients rated slow and fast brushing as equivalent in both intensity and pleasantness [3]. This has now also been shown in patients with low back pain [8]. In addition, individuals with chronic pain show reduced ability to downregulate their pain experience through competing sensations, as demonstrated in the Conditioned Pain Modulation (CPM) paradigm. Furthermore, an emerging body of research suggests that breathing slower during nociceptive stimulation is associated with reduced pain perception [32-36]. Reduced respiration rate has been shown to support the pain-relieving effects of some mind-body therapies, including meditation [37, 38]. Although there is some evidence that pleasant touch reduces respiration rate (in infants) [39], it is currently unknown whether touch-induced reductions in respiration rate mediate the pain-relieving effects of C-LTMR optimal touch. In sum, we do not know how processing of affective touch and its analgesic benefits may differ in people with chronic pain, who frequently utilize touch-based therapies in an effort to relieve their pain. The long-term goal of this research is to elucidate the sensory-affective mechanisms of light and deep touch in health and in chronic pain, in order to advance understanding of manual therapies and their effects on pain and psychological well-being.

The proposed research is the subject of a pending R00 award and will determine whether light and deep pressure touch have comparable analgesic effects, and whether these effects differ in individuals with chronic pain conditions. It will also determine which factors predict the blunted affective touch perception observed in patients with chronic pain. The central hypothesis is that both light and deep pressure touch exert analgesic benefits, and that these analgesic effects will correlate with the pleasantness of touch. Further, we predict that the analgesic effects of pleasant touch will be reduced in patients with chronic pain, who experience reduced touch pleasantness. This research will advance our understanding of the mechanisms of massage therapy and its effect on those who suffer from chronic pain.

Aim 1 (R00): Determine why individuals with chronic pain show reduced C-LTMR-related touch pleasantness.

Hypotheses: I hypothesize that blunted pleasantness of C-LTMR and deep pressure touch in individuals with chronic pain will be predicted by psychological factors including depression and trauma history (due to the impact of these factors on the μ-opioid system, e.g. [9]).

Aim 2 (R00): Determine whether the analgesic effects of light and deep pressure touch are reduced in individuals with chronic pain, and whether analgesia correlates with pleasantness perception.

Hypotheses: I hypothesize that concurrent or recent administration of light or deep pressure pleasant touch will reduce the perceived pain of a phasic heat stimulus, and that this effect will be reduced in chronic pain patients. Further, I predict that the analgesic effect of affective touch will be correlated with the perceived pleasantness of the touch.

Sub-aim 2b: Determine whether CPM effects of pleasant touch are related to CPM effects of pain.

Hypotheses: I hypothesize that the CPM efficiency for painful and pleasant touch will not be correlated across participants, suggesting divergent mechanisms.

Sub-aim 2c: Determine whether analgesic effects of light stroking or deep pressure are mediated by reductions in respiration rate.

Hypotheses: I hypothesize that changes in respiration rate will predict the analgesic (CPM) effect for pleasant touch, suggesting central modulation of pain by pleasant affect-induced changes in respiration. In addition, I predict that there will be interindividual differences in respiration at baseline that correlate with pleasantness perception and respiratory-related pain modulations.

7. BACKGROUND AND SIGNIFICANCE

Light stroking and deep pressure (compression) touch are components of numerous complementary health techniques but especially massage therapy, which has been shown to significantly reduce depression, stress, and pain [1, 10]. Deep pressure touch reduces anxiety [11] as well as induced pain and unpleasant affect [12]. Both light stroking and deep pressure have shown analgesic effects in healthy adults in a laboratory setting [6, 7]. Further, moderate (versus light) pressure is necessary for the effects of massage therapy [4], and compared to light pressure or vibration, leads to greater reduction of stress and anxiety and higher ratings of pleasantness [5]. While neutral touch is known to reduce pain perception in a segmental manner (within dermatomes) [13], the relative benefits of affective touch are unknown. Furthermore, massage therapy is a complementary therapy frequently sought out by individuals with chronic pain [14], but little is known about its analgesic benefits in individuals with chronic pain. Pleasant touch has been linked through microneurography to the activation of C low-threshold mechanoreceptor (C-LTMR) fibers, unmyelinated sensory afferents that respond to slow gentle stroking of the skin and activate opioidergic brain regions including the insula and cingulate cortex [3, 15]. We previously showed that individuals with Fibromyalgia

(FM), a chronic pain condition, show reduced pleasantness of light stroking touch. This same effect has been shown now in patients with low back pain (LBP) [8]. However, the reasons for this reduction in pleasantness of affective touch are not known. Further, it is not known whether deep pressure touch is also less pleasant for patients with chronic pain. It is also not known whether pleasant touch has a reduced (or enhanced) analgesic benefit for patients with chronic pain. There is thus a significant gap in our understanding of the processing of pleasant touch in individuals with chronic pain. The proposed R00 research will identify factors underlying the alteration of affective touch perception observed in individuals with chronic pain. Further, it will identify whether the analgesic benefits of light gentle stroking, deep pressure, and neutral touch are the same in patients with chronic pain as in healthy adults, and whether the nonsegmental analgesic effect is related to the perception of touch pleasantness. The expected contribution of the proposed research is an understanding of the analgesic effects of light and deep pressure touch in healthy individuals and in chronic pain. This contribution will be significant because it will provide knowledge of the perceptual and analgesic effects of light and deep pressure touch (components of numerous complementary therapies) in people with and without chronic pain. This contribution will inform subsequent research on manual touch therapies by providing background information about the modulation of pain by affective touch, and differences in individuals with chronic pain. This should provide greater understanding of how complementary techniques work in chronic pain.

The proposed research will compare the analgesic effects of light and deep pressure touch to those of neutral touch, determine whether the effects are direct (segmental), and determine whether these effects differ in individuals with chronic pain conditions. It will also determine which factors predict the blunted affective touch perception observed in patients with chronic pain. Finally, it will include continuous respiration monitoring during affective and pain testing to determine whether slower respiration rate underlies (mediates) the analgesic effects of pleasant touch. The central hypothesis is that both light and deep pressure pleasantness are blunted in individuals with chronic pain primarily due to psychological factors, and that the analgesic effects of pleasant touch will also be reduced in patients with chronic pain. Further, we predict that pleasant touch will exert greater (nonsegmental) analgesic benefits than neutral touch, and that this analgesic effect will correlate with the pleasantness of touch. This research will advance our understanding of the mechanisms of massage therapy and its effect on those who suffer from chronic pain.

8. PROGRESS REPORT

None, this is an initial application.

9. RESEARCH DESIGN AND METHODS

All procedures in this study are conducted solely for research purposes.

This proposed NIH-sponsored psychophysical and neuroimaging study includes two behavioral testing sessions, as well as one MRI session for a subset of participants. In this experiment we are studying sensory mechanisms supporting the modulation of pain by affective touch, and comparing them between individuals with and without the chronic pain condition Fibromyalgia (FM).

If the study will maintain a database for future uses (uses other than those specifically stated in this Research Plan), this must be clearly stated along with what information will be retained in the database and provide future examples of the potential future uses of the information.

Pre-Study Screening Procedures
Interested individuals will complete the phone screening. This includes demographic information as well as questions targeting inclusion and exclusion criteria (see Phone Screen Attachment).

Data Collection:
The following information will be collected from all participants: name, date of birth, age, gender, ethnicity, telephone number, email address, medical record number (will be deleted from study file once review of medical records is complete), diagnosis, condition, current/previous drug regimen, and handedness.

Consent & REDCap Intake

Prior to session 1, a member of the study team will email participants a REDCap link to digitally sign the consent form remotely. A member of the study team will schedule a phone or video call with participants to simultaneously discuss the consent form and answer any questions that may arise. After digitally signing the consent form and a HIPAA authorization form, history of their opiate use will be collected by asking participants to name every opiate medication they have taken previously and duration of use. Approximately one week prior to Session 1, participants will then be directed to REDCap to complete the following study questionnaires.

Study Assessments

Participants will complete the following questionnaires in REDCap:

- Chronic Pain Grade Questionnaire [16]
- Fibromyalgia Impact Questionnaire (Bennett, Friend et al. 2009)
- Childhood Trauma Questionnaire [17]
- Hospital Anxiety and Depression Scale (HADS) [18]
- Longing for Interpersonal Touch Picture Questionnaire [19]
- The Pittsburgh Sleep Quality Index (PSQI) [20]: This is a 10-item assessment designed to measure quality and patterns of sleep in adults.
- The Freiburg Mindfulness Inventory (FMI) [21]: This is a 14-item standard mindfulness scale to measure potential changes in mindfulness before and after intervention.
- Pain Catastrophizing Scale (PCS) [22]: This is a 13-item assessment derived from definitions of catastrophizing. The PCS yields a total score and three subscale scores assessing rumination, magnification, and helplessness in subjects.
- Chronic Pain Acceptance Questionnaire (CPAQ-R) [23]: This is a 20-item assessment designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce attempts to avoid or control pain and thus focus on engaging in valued activities.
- Pain Self Efficacy Questionnaire (PSEQ) [24]: This is a 10-item questionnaire that is designed to assess confidence people with ongoing pain have in performing activities while in pain.
- Social Connected Scale (SCS) [25]: This is a 20-item assessment designed to measure social connectedness, an attribute of the self that reflects cognitions of enduring interpersonal closeness with the social world, in participants.
- Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2) [26]: This is a 37-item multidimensional instrument that includes 8 scales ranging from 3 to 7 items each. The scales are noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting.
- Self-Compassion Scale (SCS): This 24-item scale measures the degree to which one is accepting of their own suffering and shortcomings, and the desire to alleviate their suffering with patience and kindness.

Consent and REDCap surveys will occur from participants' home or other remote location and will take approximately 1 hour to complete.

Session 1

When participants arrive to the laboratory for Session 1, a urine pregnancy test will be performed for all women of childbearing potential. An opiate-focused urine drug screening will also be performed. Participants who are pregnant and/or are currently taking opiates will be dismissed. A single reschedule may be permitted for a failed drug screen, if the participant identifies having consumed poppy seeds.

Participants will be fitted with a BioNomadix RSP respiratory transducer belt and amplifier. Respiration rate will be recorded with a Biopac MP160 and digitized using AcqKnowledge software at rest and throughout the entire session.

We will then familiarize participants with our touch tasks and collect baseline ratings. A brief training will be conducted to introduce sensations and rating scales. We will then collect several rounds of ratings of approximately 1 min each of light gentle brushing (using a soft paint brush), deep pressure (using a lymphedema compression sleeve inflated to <100mmHg or a commercially available massager), a neutral touch (tapping), and heat pain using a Medoc or Thermal QST thermode. Testing will occur on the limbs in areas identified as most comfortable by patients. Participants will be asked to rate their mood at various timepoints throughout the study.

Finally, we will conduct a classic CPM paradigm with a cold water bath where participants immerse their forearm into a 12°C refrigerated circulating water bath (e.g. NESLAB Digital One RTE 7, Thermo Scientific, Newington, NH, USA) for 60 seconds. The CPM paradigm is used to test the analgesic effects of a concurrent or recent test pain stimulus on a conditioned pain stimulus. The effects of the cold-CPM paradigm will be contrasted with a modified affective-CPM paradigm in Session 2. The cold-CPM block will include: phasic heat pain (baseline), heat pain while concurrently placing hand in the cold water bath (test), and then test phasic heat perception once again (post-test), as follows:

Calibration (psychophysical testing): determine level of heat to administer that results in a verbal pain rating of 6 out of 10 (0 = no pain; 10 = intolerable pain). An ascending series of 10s-duration heat stimuli between 39 and 50C will be administered until a stimulus is rated as a 6 out of 10. If a 6 is surpassed, stimuli will be decreased in .5C increments until the rating of 6 is achieved. Ratings will be confirmed by administering a 30s stimulus and adjusted if necessary.

Baseline: Heat will be administered using a thermode for 30s. Pain intensity ratings for the heat will be collected every 10s for a total of 3 ratings.

Test: 0-30s: rate unpleasantness and intensity of the cold water stimulus. 30-60s: administer heat pain using a thermode concurrently; pain intensity rating of heat pain given every 10sec for a total of 3 ratings

Post-test: Repeat of baseline.

Session 1 will occur at the ACTRI and will take approximately 1 hour to complete.

Session 2: Affective-CPM Paradigm

A urine pregnancy (if applicable) and opiate test will be performed.

Participants will be fitted with a BioNomadix RSP respiratory transducer belt and amplifier. Respiration rate will be recorded with MP160 and digitized using AcqKnowledge at rest and throughout the entire session.

We will test the analgesic effects of light slow brushing, deep pressure, and neutral touch (tapping) on induced pain using a modified affective-CPM paradigm. In this session, we will test the effect of non-painful touch stimuli on the conditioned pain stimulus, as has been conducted by [6, 7]. Both segmental (same dermatome) and nonsegmental (different dermatome) effects will be tested in order to determine whether pain inhibition is a bottom-up neural effect or an indirect affective effect.

After identifying limb locations identified as most comfortable by patients, we will perform calibration and will administer six affective-CPM blocks in an order counterbalanced across subjects: brushing, pressure, and

tapping, repeated with testing within a segment (same dermatome) and outside a segment (different dermatome).

Calibration (psychophysical testing): Session 2 calibration will be confirmed by testing the temperature rated as a 6 in Session 1 and adjusting as necessary.

Each affective-CPM block will include: phasic heat pain (baseline), heat pain with concurrent touch stimulus (test), and then test phasic heat perception once again (post-test), as follows:

Baseline: Heat will be administered using a thermode for 30s. Pain intensity ratings for the heat will be collected every 10s for a total of 3 ratings.

Test: 0-30s: rate pleasantness and intensity of the touch stimulus (brushing, pressure, or tapping). 30-60s: administer heat pain using a thermode concurrently; pain intensity rating of heat pain given every 10sec for a total of 3 ratings

Post-test: Repeat of baseline.

Between blocks the participant will rest for approximately 10-15min until sensation has dissipated to avoid habituation to test stimuli.

Session 2 will occur at the ACTRI and will take approximately 1-2 hours to complete.

Session 3: MRI Session for healthy controls (optional, offered until *N* = 20 controls have completed MRI)

A urine pregnancy (if applicable) test will be performed.

We will test the analgesic effects of affective touch on induced pain using BOLD fMRI or arterial spin labelling (ASL) in 20 healthy participants using the same test paradigm conducted in Session 2. Neural responses will be compared during the periods of thermal heat pain with versus without concurrent or recent touch.

The MRI session will occur at the UCSD Center for Functional MRI (CfMRI) and will take approximately 2-3 hours to complete.

Timeline

Sessions may be completed on the same day or on different days according to the participant and experimenters' availability. After providing written consent (active enrollment), subjects will have 4 months to complete Sessions 1 and 2 or they may be dropped from the study if the study team cannot accommodate an extension. Any spacing of sessions is acceptable. A single reschedule may be allowed for participants who fail a drug screen due to recent consumption of poppy seeds (if not previously aware) or if there are any technical issues in the session. MRI sessions will be offered to healthy volunteers until 20 have completed the MRI session. These sessions will be filled on a first-come-first-served basis.

Outcome Measure(s)

Visual Analog Scale (VAS): Pain ratings and touch pleasant/unpleasantness ratings will be assessed in response to each sensory stimulus at baseline (Session 1) and during the baseline and post-tests in the cold- and affective-CPM blocks. On each scale the minimum rating will be designated as "no pain/unpleasantness/pleasantness" and the maximum will be labeled as "most intense imaginable" or "most unpleasant/pleasant imaginable."

Cerebral blood flow (average blood perfusion; mL blood/100 grams tissue/minute): changes in cerebral blood flow (CBF) will be assessed during arterial spin labeling MRI to compare processing of pain before, during, and after affective or control touch conditions. The MRI portion of the study is a pilot study.

Sample Size Determination & Power

We expect that FM patients will show reduced pleasantness of C-LTMR-optimal touch compared to healthy individuals as found in FM patients in [3] and LBP patients in [8]. We hypothesize that current depression and trauma history will be significant predictors of blunted C-LTMR touch pleasantness. Based on an effect size F^2 of 0.15, three predictors, alpha of 0.05, and power 0.8, this study will require $N = 77$ participants. We will round up to $N = 80$ and include $N = 40$ FM patients and $N = 40$ healthy controls. Based on effect sizes observed in [3] and [8], this sample size will also be sufficient for the comparisons of pleasant touch.

Furthermore, we expect that FM patients will show reduced analgesic benefit of pleasant touch compared to healthy controls, due to reduced touch pleasantness ratings and our theorized relationship between touch pleasantness perception and analgesia, and due to reduced endogenous pain modulation evidenced in the CPM paradigm. We expect reduced analgesic effects of touch pleasantness in FM due to altered pleasant touch perception in FM (and LBP) [3, 8]. The studies showing analgesic effects of affective touch showed effect sizes of approximately $d = 0.6$ [6] and $d > 2$ (for the large compression area) [7], respectively. We would need 24 participants to demonstrate the smaller effect size in each group (alpha of 0.05, power of 0.8). No previous study has examined how pleasant touch modulates pain in chronic pain compared to healthy adults. To observe a difference in affective pain modulation between patients and healthy controls, based on the average large effect size of 0.78 seen across studies in [27] for CPM, this study would require 27 participants in each group, so the 40 participants calculated for each group will be sufficient. The MRI portion of the study will be a pilot study ($N = 20$), intended to provide preliminary data for future grant applications.

Data Analyses and Interpretation

Scores on the depression and trauma history questionnaires will be used as linear regressors to predict ratings of gentle brushing pleasantness.

Cold- and Affective-CPM: We will average the pain ratings from each stimulus period and compare the percent change of baseline to post-test ratings as our primary outcome measure. We will use ANOVA to compare differences between baseline and post-test between touch types, within or between dermatomes/segments, and between patients and healthy volunteers. A linear regression will be used to determine whether baseline touch pleasantness ratings significantly predict the CPM effect for each type of touch.

ASL/fMRI: Periods of baseline pain will be contrasted with periods of touch concurrent to pain (test) and following pain (post-test) in brain areas involved in pain processing. Connectivity analyses will be performed to identify the source of significantly reduced pain response in any of these areas during affective touch.

Inclusion of Women and Minorities:

Participants will include all genders and races. Based on the latest San Diego-based demographic consensus, we plan to recruit 60% White, 16% Asian, 7% Black, .5% Native American, .5% Pacific Islander, 12% Other race, 5% two or more races. We expect that 29% of our participants will be Hispanic or Latino. If necessary to obtain minority representation, under-represented racial groups will be targeted specifically for recruitment.

Rates of FM are higher in females than in males (9:1 ratio) [28], so an approximately 9:1 ratio is expected in the current study. All races and ethnicities will be invited to enroll. Expected demographics are based on the latest San Diego-area demographic census. If needed, to increase minority representation, recruitment efforts will include targeted advertising (e.g., flyers, postings, community outreach presentations) in communities with high minority populations and through community-based talks given by the PI and staff.

10. HUMAN SUBJECTS

Subject Population
A total of 80 adults (40 patients with FM and 40 healthy volunteers), ages 18-65, will complete the behavioral portion of the study. We will match participants with FM and healthy control participants for age and sex at the group level. In addition, 20 adults (may be same or different individuals) will complete the pilot fMRI portion of the study. We will include all genders, races and ethnicities.

Inclusion Criteria:
All participants will be:
1) Between the ages of 18 and 65 years old
2) Fluent in English

Additional Inclusion Criteria for Chronic Pain Participants:
1) Reported diagnosis of Fibromyalgia (FM) by a physician, but no other chronic pain conditions of greater pain severity (diagnosis verified by medical records whenever possible)
2) Meets 2016 revised ACR diagnostic criteria (Wolfe, Clauw et al. 2016) for FM for more than 1 year (based on phone screen)

Additional Inclusion Criteria for Control Participants:
3) no indication of current pain or chronic pain (based on phone screen)

Exclusion Criteria:
1) Sensory, motor, or anatomic differences or injuries relevant to study procedures
2) Known anomalies of the central nervous system (including stroke, dementia, aneurysm, or personal history of psychosis)
3) Pregnancy
4) Inability to rate pain or sensations
5) Major medical conditions such as kidney, liver, cardiovascular (hypertension, preexisting cardiac arrhythmia), autonomic, pulmonary, or neurological problems (e.g., seizure disorder) or a chronic systemic disease (e.g., diabetes).
6) History of blood clots or clotting disorders
7) Current use of opiate medication(s)
8) Contraindications to MRI if participating in pilot MRI study
9) Unable to identify a heat stimulus 50C or lower that generates a rating of a 6 on our VAS scale
10) History of fainting or seizures
11) History of frostbite
12) Open cut or sore on hand to be immersed in cold water bath
13) Fracture of limb to be immersed
14) History of Reynaud's phenomenon (hands get white, then blue on exposure to cold, then red on warming)

We will recruit healthy controls (HC) that are group-matched to the chronic pain (FM) patients by age and sex.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Subjects will be recruited through four primary methods: (1) from IRB approved flyers and recommendations by UCSD study physicians, (2) the ResearchMatch website, (3) via patient information extracted from EPIC, and (4) through web advertisements on social media and websites. We will begin study recruitment after we have completed all NIH oversight requirements.

1) We may post IRB approved flyers throughout the community and UCSD Pain Medicine physician offices. If a physician believes a patient is qualified for this study, they will refer the potential participant

to the flyer at which point they can voluntarily contact the research team to assess eligibility. In addition, the treatment physician may approach the participant and introduce the study. The treating physician will further discuss the research study with the potential participant and refer them to the research team's contact information, at which point the patient has the discretion to contact the study staff. There will be no direct contact of the potential research subject by the study staff unless prompted by the potential subject. Their treating physicians can refer them to our study and they will call us, if they choose, on their volition. We will not access medical records until after we have permission.

2) The study may be advertised on ResearchMatch to gain interest for participation. This site will allow for members of the community to inquire as to their potential interests in the study's goals and requirements.

3) We may request a Data Extraction Concierge Service (DECS) through the ACTRI. The service will allow ACTRI staff to extract patient information from Epic and find participants that may be eligible to participate in the study. The exported data will include: patients' MRN, name, phone number, mailing address, and email address. These patients may be contacted by phone, a mailed hard copy letter, and/or by email (containing no PHI). No more than two methods will be used per patient (methods will depend on response rate we identify in practice).

4) We may post study advertisements on social media and websites either ourselves, or through BuildClinical. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the U.S. to ensure they adhere to all the appropriate guidelines and procedures and are approved and currently in use by multiple colleagues in the UC San Diego School of Medicine. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc. and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps participant information private, and is HIPAA compliant. Their backend servers are stored in the USA at some of the most secure data centers in the world. This strategy will allow us to target potential chronic pain participants and provide preliminary screening procedures for individuals who may be eligible to participate in the study. Contact information will include name, phone number, and email. BuildClinical retains the information in their portal throughout the duration of the contract. Upon termination of service, the information is deleted from the portal and it may be downloaded as an excel file to keep for our records. The information is transferred through their HIPAA Compliant platform that encrypts all data in transit and at rest. There is 2 factor authentication available for use and every researcher will have their own unique login credentials. Ad targeting will be for ages within our 18-65 range and for the San Diego geographic region. BuildClinical will refine ad targeting based on the profiles of persons who click on initial ads. We have uploaded as supplementary materials our lab's social media ad as well as all materials from BuildClinical (screening form, ad copy, ad creatives, and landing page).

When a potential subject contacts our lab, a brief subset of preliminary eligibility criteria (such as age, gender, etc.), will be reviewed by study personnel to determine subjects' preliminary eligibility for the research study during the phone screening and Visit 1. The attached phone script will be employed to identify preliminary study eligibility. The study team member screening potential subjects will obtain verbal consent before any subject information is collected. See item 12 below for request for waiver of documented consent for this screening. Subjects who fulfill the preliminary eligibility criteria will be offered further participation in this study.

Preliminary eligibility may be determined at the time of phone screening, but formal eligibility will only be determined after informed consent is obtained and a standard, stand-alone HIPAA authorization form is

signed. Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent during Session 1. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log. The Screening/Enrollment Log is necessary to keep track of who the subjects enrolled in the study are, and record their responses to the screening questions for use in describing the study sample in any resulting publications. No entries will be made in the Screening/Enrollment Log for individuals who do not pass screening or do not consent and provide HIPAA authorization. The study funder (NIH) will not have access to the subject's PHI. Only team members, as described in item 21, will have access to this information.

Strategies: Diversity and reflection of regional population. Geographically, the clinics at the Altman Clinical and Translational Research Institute service a broad portion of the greater San Diego region. As a result, our study coordinators will recruit patients from a highly diverse patient population in terms of race, gender, and socioeconomic status. Subject populations in previous and ongoing studies have reflected the diversity of the region and disease-specific demographics. If we are unable to obtain sufficient minority representation in our sample, under-represented racial groups will be specifically targeted for recruitment.

Contingency plans: Should the above streams of recruitment prove inadequate for us to meet our accrual timetable and keep our cohort schedule on track, we will reach out to social media and other local print and multi-media-based advertisement strategies prominent within the San Diego area. This approach has proved useful in past studies and should do so again. Participants will also be reimbursed for successful study completion. This approach has been useful in motivating participants to complete their study responsibilities in the past. If we find that the amount offered is inadequate for maintaining active subject engagement, we will consider increasing it.

These recruitment plans have been very successful at attaining targeted sample sizes in previous studies and have been recognized by UCSD and the NIH as appropriate models for recruitment success. The Research Plan will be amended to include these recruitment strategies or materials as they are added but prior to their use.

ResearchMatch message text is submitted separately. Other recruitment materials that are not included in this submission will be submitted to and approved by the IRB prior to use.

12. INFORMED CONSENT

Waiver of Documented Consent for Aiding in Determining Preliminary Eligibility during Research Recruitment:
We are asking for a waiver of documented consent while recruiting subjects to appropriately identify potential subjects during the phone screening procedure. The phone screen is considered no more than low risk to the potential subjects, since we will not perform any procedure, and the probability and magnitude of harm or discomfort anticipated in this research are not greater than those ordinarily encountered in daily life. In addition, our methods of recruitment do not allow the pre-screener to directly contact or call the patient unless the patient, themselves, contacts the study team first through contact information provided on study advertisements or the patient's treating physician refers them to the study.

The information inquired about and collected from the phone screen is necessary to ascertain the potential subject's suitability for entry into the study. While reviewing responses and information during the phone screen, the screener may determine that the potential subject qualifies for the study and then proceed to ask if they would be interested in participating. The screener will indicate to potential subjects that review of their medical records will be involved in determining formal study eligibility.

If a subject qualifies for the study, information collected from the phone screens will be entered into two separate password-protected databases: one for personal identifiable information, and one containing the participant's responses. In the second database, the subject will be identified with a recruitment number that is determined simply by the order in which subjects contact us. This second database, linking participants' personal identities to code numbers will be stored in locked research files separately from research records. Thus, the hard copy Phone Screen will be shredded immediately for subjects who do not qualify, and after the information has been entered into our password-protected databases for subjects who do qualify (after written consent is obtained). The Phone Screen (excluding the page with contact information) will be labeled with the recruitment number, which will also be used to link the two databases. Hard copies of screening responses will be labeled only with the date and the participant recruitment number.

Consenting Procedures:
Once a potential study participant expresses interest in our study and meets preliminary eligibility requirements, as determined by phone screening, the subject will be asked to digitally provide consent via REDCap, using an IRB-approved consent form, approximately one week before their first study session. The consent process will take place prior to performing any study related procedures. While participants have the consent form open in REDCap, a study team member will call participants by phone or video to describe the study, including detailed information about risks and benefits, and answer questions. The study team member will provide potential subjects with an IRB-approved consent form in REDCap. Potential subjects will be given ample time to read this consent form or may request to read it at another time. Potential study subjects will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, or the consent form itself before digitally signing the consent form. As this research is subject to HIPAA privacy rule provisions, subjects will also be requested to digitally sign a separate HIPAA authorization in REDCap for the use of protected health information. Participants will have the opportunity to download a signed copy of the consent and HIPPA authorization forms for their records.

Over phone or video, questions will be asked and elicited in order to ascertain that participants comprehend the study procedures as well as potential risks involved, prior to consenting to the study. All study related questions from study participants that a research staff member is unable to address will be referred to the Principal Investigator, or other co-investigators. No clinical information beyond screening (extended phone screen and clinical information) will be gathered until participants have provided written, signed informed consent.

Potential subjects who fulfill the eligibility criteria will be offered further participation in this study. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

All digitally signed consents will be maintained in REDCap and on laboratory password protected computers and servers, as well as in marked binders secured in locked filing cabinets within private offices at Dr. Zeidan and Case's Laboratory at the ACTRI. Documentation of this process will be written form and placed in the research record. A copy has been uploaded for IRB review and approval.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participation in this study is not to participate.

14. POTENTIAL RISKS

This study may involve some risk, although the risks are considered minimal.

Risks of Psychological and Cognitive Assessments:
The main risks are that clinical interviews, cognitive testing and self-report questionnaires are time-consuming. Material elicited during interviews may be upsetting to some study participants. Others may find cognitive tasks to be challenging or frustrating. These assessments, however, rarely pose psychological risks for study

participants.

Risks and discomforts associated with heat pain stimuli:
Reddening/darkening of the skin may occur with thermal stimulation; this is transient and disappears after termination of the testing. The heat stimuli, which are of moderate to strong intensity, will not damage the skin. Heat pain stimulation has been used extensively without any long-term adverse effects and do not cause permanent tissue damage [29-31].

Risks and discomforts associated with cold water bath task:

The cold water bath is a commonly used pain task and is considered safe [39], However, it is possible (although rare) that a participant might react to immersing their hand in the cold water with a stress response, that is, increased heart rate and/or, in extreme instances, fainting. It is also possible that discomfort and numbness of the hand may occur during and after submerging it into the cold water bath. This is temporary and will not damage the skin..

Risks and discomforts associated with brushing and compression stimuli:
There are no known risks of the gentle brushing. Pressure stimuli may be uncomfortable to some participants, but the pressure will be lower than a standard blood pressure cuff and thus familiar to all participants. Repeated compression could theoretically dislodge any active blood clots in the participant's limb.

Risks for screening and questionnaires:
We have included a number of validated questionnaires to assess variations across individuals. Some of these items include sensitive questions about one's psychological and health state.

Risks of MRI and fMRI:
People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware.
It is not known if MRI is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.

People with fear of confined spaces (i.e. claustrophobia) may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. There are no known long-term risks of MRI scans.

Risk of Breach of Confidentiality:
There is a risk that information collected in our study could become known to individuals not involved in our study. MRI data are not used for diagnostic purposes and all data are associated only with identification numbers. Breaches in confidentiality could impact future insurability or employability. However, in our experience, this has not occurred with this type of research.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Privacy of participants:
Research staff will be trained by the PI to respect the privacy and confidentiality of NIH employees and staff, especially with regard to sensitive, private information. All data will be de-identified and personnel will not view data alongside identifying information, which will reduce the possibility that lab personnel would be able to associate sensitive information with individuals. The lab will discuss professionalism and confidentiality, and if

lab personnel are acquainted with any potential participants, a different investigator will interact with that participant.

Confidentiality of Data:
We will actively protect confidentiality of the subjects and the data at each step. All medical records and subject data will be kept confidential and will only be reviewed by the participating investigators. Data will be de-identified and stored using codes that we assign. De-identified data will be kept on password-protected computers or in locked cabinets at UC San Diego. Only study investigators will have access to the data.

Psychological risks:
Participants will be informed that they can skip any questions they do not wish to answer, and that participation is voluntary. If participants are triggered by items on study questionnaires, they will be offered a break to disengage from the task and asked whether they wish to continue or not. If participants remain upset referrals to psychological care at UC San Diego will be made.

MRI:
Subjects will be screened for the conditions described in the "Risks of MRI and fMRI" section before having any scan, and if they have any, they will not receive an MRI scan. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room. Subjects will be fitted with hearing protection. Subjects will be instructed to let us know right away should the hearing protection come loose during the scan. Subjects will also be instructed to notify the investigators if they have hearing or ear problems. Subjects will be asked to complete an MRI screening before having the MRI.

Sensory stimuli:
Sensory testing procedures and risks will be described carefully and participants will be encouraged to provide immediate feedback if a stimulus is not tolerable. All participants will be screened to ensure they do not have any history of blood clots of first degree family members with clotting disorders.
All risks to subjects are minimal and unlikely to have significant impact. If subjects are injured by study procedures they will be evaluated by the study physician will be treated by care providers at UC San Diego. Incidental findings such as from MRI will be shared with the subject by a medical provider affiliated with the study and appropriate referrals for follow-up care will be made.

Cold water bath:
Participants will be instructed and reminded that they can remove their hand from the cold water in the event they find it intolerable or do not wish to continue.

Monitoring:
An Independent Monitor (IM) will monitor the activities of this study for purposes of evaluating participant safety and study integrity. The study PI will oversee all experimental procedures of the proposed research activities. In the event of an adverse safety event, protocol deviations and adverse events will be promptly (less than 24 hours) reported to the IMC and the IRB.
This study will follow the Data and Safety Monitoring Plan submitted to NCCIH for the proposed R00 award:

Adverse Event (AE):
An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

Unanticipated Problems (UP):

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Event (SAE):
A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Time Period and Frequency for Event Assessment and Follow-Up:
Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events occurring during the testing session or reported by the participant to the PI within 30 days of the testing session. If participating in multiple study session, at each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Characteristics of an Adverse Event Relationship to Study Intervention:
To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

Expectedness of SAEs:
The Study PI and Independent Monitoring Committee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

Severity of Event:
The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

Unanticipated Problem Reporting:
Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

Adverse Event Reporting of Non-IND Studies:
SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

Halting Rules:
The study will be halted Halt if any SAE related to study participation or two severe AEs/reactions occur, until a complete safety review is convened.

Measurement and Reporting of Subject Accrual:
Review of the rate of subject accrual will occur monthly during the recruitment phase to ensure that a sufficient number of participants are being enrolled, in keeping with proposed recruitment projections, and that they meet eligibility criteria and fulfill the targeted ethnic diversity goals outlined in the grant proposal.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Study recruitment and enrollment will be monitored through a Screening/Enrollment Log, both created as password protected Microsoft Excel spreadsheets. No identifying information will be used on any study documents after enrollment. Enrolled subjects will be assigned a unique subject identification number (SID)

that will be used on all Case Report Forms (CRFs) and study related documents after enrollment. The SID will be linked to subject identifiable information only in the Screening/Enrollment Log, created and password protected in a Microsoft excel spreadsheet. This will be stored on a coordinator's password protected and encrypted computer in the ACTRI.

To minimize possible risk of breach of confidentiality, the SID will be used for each subject as the unique identifier for all research related activities. All information collected, including self-report questionnaires, psychological assessments, and sensory data will be identified solely by the SID and without any personal identifiers. Electronic data will be stored on password protected computers on servers in the ACTRI. Only strictly anonymous data will be entered into electronic databases and used for statistical analysis. Access to the participant numbering system will be limited to the Principal Investigator and the research staff involved in the study. Research files will be kept in locked cabinets or drawers in a locked office or clinic or storage room, in the ACTRI, and made available only to qualified personnel for research purposes. No verbal or written information concerning a subject will be released to anyone without expressed written consent by the subject. Any data shared with the sponsor will be transferred electronically with no identifiers whatsoever.

As part of consent procedures, participants will be advised of precautions taken to preserve confidentiality. Further, all individuals involved in data collection procedures will be instructed to not divulge any information concerning participants to any person or agency without the written and explicit consent of the patients. These procedures have been effective in completely protecting patient information in past studies. All study staff receive Good Clinic Practice and Human Subjects Protection training as well as HIPAA privacy training before working with any participants. No published or presented materials will identify patients by names, initials, or any other means that could be used to identify the participant.

Recruitment will take place from private office and clinic areas. Recruitment will not take place in an open public area, hallways, a crowded waiting room, or other venue that would jeopardize participant privacy. The informed consent process will take place in a private room at the ACTRI where the participant can ask questions without feelings of embarrassment or discomfort.

17. POTENTIAL BENEFITS

There are no direct benefits from participating in this study. Each participant will receive financial compensation for participating in the study, but all participants will be informed that there are no direct benefits to them for participating in the research study.

Study participants may gain satisfaction from the knowledge that they are contributing to a better understanding the neurobehavioral underpinnings of chronic pain.

18. RISK/BENEFIT RATIO

There are no alternative procedures that will provide comparable information to that obtained by the methods described in this study. The risks for this study are small in comparison to the substantial anticipated benefits regarding better understanding of chronic pain.

19. EXPENSE TO PARTICIPANT

There will be no expense to the participant except for their transportation and parking.

20. COMPENSATION FOR PARTICIPATION

Participants will receive $60 for intake/Session 1 and $60 for Session 2 for a total of $120. The subset of subjects participating in the MRI session will receive $120 for the MRI session. A free parking voucher code

will be made available for each study session. If a reschedule is needed, subjects will receive prorated compensation for any partial sessions completed.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All personnel will be trained by Dr. Case or Dr. Wallace and/or Dr. Chakravarthy (when needed) to perform their respective study procedures before any participants are screened or enrolled.

Dr. Laura Case— Principal Investigator

- Role/Responsibilities:
  - Oversees all study members, procedures, information, and research activities. She can and may review medical record history to confirm diagnosis.
- Qualifications/Certifications/Licenses:
  - CITI Training in Biomedical Research and Good Clinical Practice
  - PhD in Experimental Psychology
  - Postdoctoral training in pain research and brain imaging

Dr. Krishnan Chakravarthy, MD, PhD – Co-Investigator

- Role/Responsibilities:
  - Consulting study physician and can and may review medical record history to confirm diagnosis.
- Qualifications/Certifications/Licenses:
  - CITI Training in Biomedical Research and Good Clinical Practice
  - California Medical License to practice as a Physician and Surgeon by the Medical Board of California

Dr. Mark Wallace, MD — Co-Investigator

- Role/Responsibilities:
  - Consulting study physician and can and may review medical record history to confirm diagnosis.
- Qualifications/Certifications/Licenses:
  - CITI Training in Biomedical Research and Good Clinical Practice
  - California Medical License to practice as a Physician and Surgeon by the Medical Board of California
  - Clinical trials expert

Dr. Thomas Liu, MS, PhD — Co-Investigator

- Role/Responsibilities:
  - Consulting MRI expert for all fMRI related procedures of the study at the CfMRI.
- Qualifications/Certifications/Licenses:
  - CITI Training in Biomedical Research and Good Clinical Practice
  - PhD in Electrical Engineering

Dr. Nathaniel M. Schuster, MD – Co-Investigator

- Role/Responsibilities:
  - Consulting study physician and can and may review medical record history to confirm diagnosis.
- Qualifications/Certifications/Licenses:
  - CITI Training in Biomedical Research and Good Clinical Practice
  - California Medical License to practice as a Physician and Surgeon by the Medical Board of California

Dr. Benedetta Albinni – Post-Doctoral Researcher

- Role/Responsibilities:
    - Assists to oversee all study members, procedures, information, and research activities. She can and may review medical record history to confirm diagnosis. She will assist with all aspects of the study, including coordinating, collecting data, and conducting sensory testing across all study sessions. She may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. She will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and collect self-report information (including PHI).
- Qualifications/Certifications/Licenses:
    - CITI Training in Biomedical Research and Good Clinical Practice
    - PhD in Cognitive Neuroscience

Michael Haupt, Graduate Student – Research Assistant

- Roles/Responsibilities: Mr. Haupt will assist with data collection and conducting sensory testing across all study sessions. He will also assist with data analysis.
- Qualifications/Certifications/Licenses:
    - CITI Training in Biomedical Research and Good Clinical Practice
    - MA in Quantitative Methods in the Social Sciences

Marisa Zimmerman, BS in Cognitive and Behavioral Neuroscience – Research Assistant

- Roles/Responsibilities: Ms. Zimmerman will assist with all aspects of the study, including coordinating, collecting data, and conducting sensory testing across all study sessions. She may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. She will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and collect self-report information (including PHI).
- Qualifications/Certifications/Licenses
    - CITI Training in Biomedical Research and Good Clinical Practice
    - BS in Cognitive and Behavioral Neuroscience

Vincent Alasha, BA in Psychology – Research Assistant

- Roles/Responsibilities: Mr. Alasha will assist with all aspects of the study, including coordinating, collecting data, and conducting sensory testing across all study sessions. He may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. He will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and collect self-report information (including PHI).
- Qualifications/Certifications/Licenses
    - CITI Training in Biomedical Research and Good Clinical Practice
    - BS in Cognitive and Behavioral Neuroscience

Jeffery Lewis, UCSD student in Cognitive Behavioral Neuroscience – Research Volunteer

- Roles/Responsibilities: Mr. Lewis will assist in all aspects of the study including coordinating, collecting data, and conducting sensory testing across all study sessions. He may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. He will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and can collect self-report information (including PHI).
- Qualifications/Certifications/Licenses

- CITI Training in Biomedical Research and Good Clinical Practice
- Undergraduate in Cognitive Behavioral Neuroscience

Leyla Ozdoyuran, UCSD student in Psychology – Research Volunteer

- Roles/Responsibilities: Ms. Ozdoyuran will assist in all aspects of the study including coordinating, collecting data, and conducting sensory testing across all study sessions. She may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. She will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and can collect self-report information (including PHI).
- Qualifications/Certifications/Licenses
  - CITI Training in Biomedical Research and Good Clinical Practice
  - Undergraduate in Psychology

Jacob Ross, UCSD student in Neurobiology – Research Volunteer

- Roles/Responsibilities: Mr. Ross will assist in all aspects of the study including coordinating, collecting data, and conducting sensory testing across all study sessions. He may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. He will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and can collect self-report information (including PHI).
- Qualifications/Certifications/Licenses
  - CITI Training in Biomedical Research and Good Clinical Practice
  - BS in Neurobiology

Lillian Xia, UCSD student in Psychology – Research Volunteer

- Roles/Responsibilities: Ms. Xia will assist in all aspects of the study including coordinating, collecting data, and conducting sensory testing across all study sessions. She may also assist with recruitment methods, including in-person recruitment at the UCSD pain clinic, conducting phone screenings, consent procedures, HIPPA authorization, randomization, scheduling, and acting as a communication point for the study. She will help maintain IRB binders and corresponding duties and can and may review medical records to confirm diagnosis and can collect self-report information (including PHI).
- Qualifications/Certifications/Licenses
  - CITI Training in Biomedical Research and Good Clinical Practice
  - Undergraduate in Psychology

We will likely hire another (TBD) post-doctoral fellow or research assistant to help with the data collection.

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An administrative supplement is anticipated, awaiting NOA.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON STAFF

Not applicable.

27. CONFLICT OF INTEREST

The PI and all key personnel report no conflicts of interest.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Those trained to screen subjects will be responsible for determining the decisional capacity of the subjects being considered for inclusion in the protocol. During the consent process, those screening subjects will reiterate study details and will assess for an understanding of the required study involvement. These details include the nature of pain tasks, the duration of study, and maximum and partial compensation. If the decisional capacity is questionable, further evaluation will be performed and documented in regard to this matter. If the investigator determines that the subject lacks decision-making capacity, they will not enroll the subject into the study.

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