Peripheral Oxytocin and Touch (POPP)

NCT05326776

Study Consent:

Version date: 9/11/2023

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Version date: 9/11/23

1. PROJECT TITLE

Effect of Peripheral Oxytocin on Touch Pleasantness and Pain

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

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4. ESTIMATED DURATION OF THE STUDY

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

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

Research shows that slow gentle skin stroking can activate special sensory nerves in the skin that elicit relaxing effects on the body and mind, similar to the effects of the hormone oxytocin. Studies also suggest that gentle stroking may even release oxytocin in the skin. However, we do not know what oxytocin does in the skin and how it affects nerves that send pleasant touch or pain signals to the brain. The proposed study will determine how individuals perceive gentle stroking and experimental pain before and after a skin injection of oxytocin compared to a placebo injection. This research will determine the role of oxytocin in affective touch and pain perception and whether it may have clinical potential to relieve pain.

6. SPECIFIC AIMS

Aim 1: Assess whether subcutaneous injection of oxytocin versus saline placebo has local anti-nociceptive effects on experimental pain.

Hypotheses: We hypothesize that OT will reduce pain threshold and ratings of pain intensity and unpleasantness for thermal, mechanical, and pressure pain.

Aim 2. Assess whether subcutaneous injection of OT versus saline placebo alters local pleasantness of CT gentle stroking.

Hypotheses: We hypothesize that OT will increase touch pleasantness of slow versus fast stroking and will increase heart rate variability.

7. BACKGROUND AND SIGNIFICANCE

Given the major burden of chronic pain in the U.S.[1,2], there is an urgent need to understand basic mechanisms of chronic pain and develop effective interventions, including nonpharmacologic approaches like massage. While massage is widely sought for its effects of pleasant relaxation and pain reduction[3], the neural mechanisms underlying affective touch and its effects on pain are poorly understood. A clear understanding of basic pathways for touch-based therapies is needed to understand the mechanisms of their effects on pain and mood, determine changes in chronic pain conditions, and identify potential targets for noninvasive modulation of affect and pain.

Thickly myelinated Aα and Aβ afferent sensory fibers rapidly conduct proprioceptive and touch signals to the brain, while thinly myelinated Aδ and unmyelinated C-fibers transmit temperature, chemical, and pain signals at a slower speed[34]. A large body of evidence demonstrates that a subset of unmyelinated C-fibers known as C-tactile (CT) afferents project to the insula and convey the pleasant sensation of stroking on hairy skin[4-7], leading to theories of a privileged CT pathway for affective touch[4,8] as well as pain reduction[9]. As predicted by this model, patients with reduced C-fiber afference show reduced preference for slow stroking[10], while patients with myelinated A-fiber deafferentation retain its pleasantness and insula response[4]. Furthermore, slow (CT-

optimal) versus fast touch induces affective alterations including positive mood[4,5] and increased heart rate variability[6].

Oxytocin (OT) is a neuropeptide broadly implicated in social behavior[7]. Systemic administration of OT reduces stress and anxiety and increases trust[8]. In addition, OT exerts antinociceptive and analgesic effects in both humans and rodent models[9,10]. Given the similar effects of CT stimulation and systemic OT, OT is a proposed mediator for the affective effects of CT touch[11]. Indeed, stimulation of sensory afferents induces OT release[12,13], and intranasal OT increases touch pleasantness[14]. OT directly modulates wide dynamic range neurons in the spinal cord and C-fiber excitability[15,16]. These mechanisms may be engaged by social skin touch[17], potentially mediated by keratinocytes[17]. Recent research in rodents demonstrates that OT also exerts powerful effects in the periphery, where OTRs on nociceptive terminal axons can inhibit nociceptive input.[18] Indeed, injection of OT into the paw reduced pain behavior in a neuropathic pain model, selectively in the injured paw[19]. Furthermore, in mice, OT injected in the ganglion reverses hypersensitization of HTMRs and hyperpolarization of LTMRs that is induced by nerve injury[20]. These studies demonstrate a local modulation of pain by peripheral OT.

OT is not used clinically because it cannot penetrate the blood-brain barrier, has poor specificity and a short duration of effect, and cannot be patented[21]. However, only one study has tested the effect of peripheral OT in humans, demonstrating reduced postsurgical pain after subcutaneous OT injection prior to gallbladder surgery[22]. The OT group (N = 10) received subcutaneous OT (Oxitopisa, 4µg in 4ml of saline) in each of the surgical sites before surgical incisions were made. Pain was marginally reduced after surgery (Cohen's d = 3.53) and was significantly reduced upon discharge (Cohen's d =4.16) and 24 hours after surgery (d =4.51)[22]. These effects have not been tested in healthy adults undergoing acute pain. These findings reveal a significant gap in our understanding of the role of peripheral oxytocin in the pathways for affective touch and pain.

Effects of OT on pleasant touch have been tested through the intranasal route of administration. Chen and colleagues tested the effect of 24IU intranasal OT on 40 male subjects in a cross-over design administering positive, neutral, and negative valence touch on the arm with velocities targeting C-tactile afferents[23]. OT significantly increased touch pleasantness ratings independent of touch valence (estimated Cohens d = 3), with the effect largely driven by negative stimuli. This study provided the first evidence that OT may enhance rewarding effects of touch, regardless of valence. In addition, the same group administered manual or machine foot massage to 46 male participants. Intranasal OT significantly increased pleasantness ratings for manual massage, supporting the importance of OT for enhancing positive responses to social touch[14].

The proposed ACTRI pilot research project will identify the effect of subcutaneous oxytocin on experimental pain and pleasant CT stroking. This contribution will be significant as it will provide foundational knowledge about the role of peripheral OT in perception of affective touch and pain. This is important because pathological states alter affective touch perception[29,31-33] and may involve corresponding changes in the role of peripheral OT in affective touch pathways, with potential significance for therapeutic use of peripheral OT. The central hypothesis is that OT will reduce pain threshold and ratings of pain intensity and unpleasantness for thermal, mechanical, and pressure pain. Further, we predict that OT will increase touch pleasantness of slow versus fast stroking and will increase heart rate variability. This research will advance our understanding of the mechanisms of touch-based therapies, such as massage, and identify potential targets for noninvasive modulation of affect and 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 study includes one baseline calibration session and two experimental testing sessions. To experimentally manipulate local OT in the skin, we will test the effects of subcutaneous injection of OT on the perception of acute pain and affective touch by comparing double-blind injection of 4mcg/2ml OT and isotonic saline placebo (2ml) on pain perception.

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

Consent
Inclusion/exclusion criteria will be confirmed at the start of each session before consent is signed. Consent will be administered in-person in the ACTRI clinic at UCSD, at the beginning of Session 1. A member of the study team will discuss the consent form and answer any questions that may arise.

Baseline measures:

After consent is signed, basic demographic data will be confirmed from the phone screen record and logged in study records (name, date of birth, age, gender, sex at birth, ethnicity, race, telephone number, email address, current medications, and handedness). Current medications will be reviewed and updated at the beginning of each session. Participants will be asked questions regarding their recent food, alcohol, and caffeine intake, smoking, exercise, and sleep to assess as study covariates.

Study Questionnaires
Participants will complete the following questionnaires in REDCap:

- State-Trait Anxiety Inventory (STAI): This is a 40-item scale that measures both state and trait anxiety[68].
- Pain Anxiety Symptoms Scale (short form PASS-20): This is a 20-item scale that assesses fear in association with pain[69,70].
- 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.
- Body Awareness Questionnaire (BAQ): This 18-item scale measures attention to bodily processes[72,73]
- The Autism Quotient (AQ): The AQ has been observed to negatively correlate with baseline OT concentrations[23].
- Adapted version of Longing for Interpersonal Touch Questionnaire: This questionnaire assesses touch received and desired in the last week. This questionnaire has been modified to remove gendered language.

Heat pain calibration
Ratings of heat stimuli will be collected to determine a moderately painful heat stimulus for use in pre- and post-sensory testing. Ascending and descending series of 10s heat stimuli (32-50°C) will be presented on the arm until pain intensity is rated '70' on the visual analog scale (VAS) pain intensity scale.

Baseline measures will occur at the ACTRI and will take approximately 30 minutes to complete.

Sessions 1 and 2/ Sensory testing with oxytocin or saline

Participants will be greeted and seated in a comfortable reclining position.

Urine pregnancy test: Due to the risks of OT on a pregnancy, participants with the potential to become pregnant will undergo a urine pregnancy test at the beginning of both sessions. Participants with a positive pregnancy test will be dismissed.

Baseline assays for peripheral oxytocin , inflammation, and metabolic features: Blood (approx. 10mL) will be collected from all participants at the beginning of Sessions 1 and 2 to conduct ELISA immunoassay to measure baseline OT concentrations, as well as baseline IL-6 (a pro-inflammatory cytokine) and metabolic features (approx. 20mL blood drawn total in study).

Baseline heart monitoring: Participants will then undergo a 5-min baseline monitoring period during which resting heart rate will be monitored, using a Bionomadix wireless ECG system from Biopac (or equivalent). Heart rate will be continuously recorded in a time-locked manner throughout the session and used to calculate heart rate variability during affective touch and pain in either session.

VAS measures:

Participants will be asked to make the following ratings throughout the session:

Intensity of the touch sensation: “No sensation” (far left) to “Most intense sensation imaginable” (far right)

Unpleasantness of the touch sensation: “Extremely unpleasant” (far left) to “Neutral” (middle) to “Extremely pleasant” (far right)

Pain intensity: “No pain” (far left) to “Most intense pain imaginable” (far right)

Pain unpleasantness: “Extremely unpleasant” (far left) to “Neutral” (middle) to “Extremely pleasant” (far right)

Skin monitoring: Photos will be taken of the participant’s arm before and after injection to document the possibility of any adverse response. Photos will not show any other part of the body other than the arm and will be deleted from the smartphone the same day as the session and stored on secure computers by subject ID, like our other PII. In the case of an adverse reaction, the study physicians will grade the severity of reaction as advised by the FDA.

Pre-sensory testing

Anxiety ratings will be collected using VAS rating scales for fear of pain (1 = “no fear of pain” to 100 = “extreme fear of pain”) and state anxiety (1 = “extremely calm” to 100 = “extremely anxious”)

Affective touch perception:
Affective touch testing will be comprised of 2 trials of 15s slow brushing and 2 trials of 15s fast brushing on each dorsal forearm, in a random order. After each trial participants will rate the (un)pleasantness and intensity of the sensation on VAS scales.

Pain perception:
Mechanical pain threshold (MPT): MPT will be determined using weighted pinprick stimuli exerting forces of 8, 16, 32, 64, 128, 256 and 512 mN[24]. Stimuli will be applied for 2s on and 2s off until the first percept of sharpness (pain) is reported.

Temporal summation: Temporal summation will be tested using a standard 256mN pinprick stimulus applied for 10 repetitions of 1s each, over the same 1cm² area[24]. The participant will provide pain ratings for a single

pinprick and for the 10 repetitions, using the VAS rating scales described above. This procedure will be repeated 3 times and the mean pain rating used.

Pressure pain threshold (PPT): PPT will be tested using a pressure algometer placed over the dorsal forearm muscles (e.g. extensor digitorum), and pressure will be increased until pain is reported[25].

Heat pain threshold (HPT): HPT will be tested using a high-quality QST thermode. To establish HPT, the thermode will be placed on the arm at a baseline of skin temperature (automatically calibrated by the thermode) and will be increased until the stimulus is reported as painful by the participant[24]. The mean of three trials will be taken as the HPT.

Heat pain ratings: Three 10s trials of the individually calibrated pain-70 heat stimulus will be rated using the VAS rating scales for pain intensity and (un)pleasantness described above.

Injection of Oxytocin or saline control: Either 4mcg/2ml OT ***OR*** 2ml isotonic saline (0.9% sodium chloride; placebo control) will be injected into the middle of the dorsal forearm. Sessions will be separated by at least 48 hours to ensure drug clearance[19,26]. Both participants and experimenters will be fully blinded with respect to OT versus saline placebo session/order. OT and saline will be prepared by the Investigational Drug Service at the ACTRI. OT will be prepared by diluting commercially available synthetic oxytocin (OXYTOCIN- oxytocin injection, solution from Fresenius Kabi USA, LLC or equivalent manufacturer supplied by the ACTRI research pharmacy; see uploaded package insert). The injection will be performed by a licensed healthcare provider. Saline placebo will be drawn from SODIUM CHLORIDE- sodium chloride injection, solution from B. Braun Medical Inc or equivalent manufacturer supplied by IDS pharmacy (see uploaded package insert).

Blood pressure and oxygenation will be monitored before and after OT injection and at approximately 5 minute intervals (BP) or continuously (pulse ox) for the remainder of the session.

Post-sensory testing: Perception of pain and gentle brushing will be tested beginning ~10min after injection on the injected arm, given timing of OT effects in prior studies[18-20], and then on the control arm. A post-block baseline sensory test will be conducted, identical to the affective sensory testing described above. All testing will be conducted within a ~3-4cm^2 sized region of skin proximate to the injection site on the dorsal forearm. At the end of testing, the injected arm will be observed by a licensed provider to confirm normal sensation and lack of any adverse response to OT injection.

Sessions 1 (after baseline) and 2 will occur at the ACTRI and will take approximately 1 hour each to complete.

Participant Randomization:

The schedule of randomization will be created and accessed by an ACTRI pharmacist only. Males and females will be randomized without replacement across a block of 20 codes (assuming 20% attrition) using an Excel-based random number generator. All subjects will receive OT in one session and saline placebo in the other in this within-subject cross-over study. Subjects will be randomized to one of two session orders (Session 1 OT and Session 2 saline; Session 1 saline and Session 2 OT). Randomization will be stratified so that each sex will have their respective list of randomization codes. Session order (blinded code) will be tracked in the Screening/Enrollment Log maintained by the study coordinator(s) and identity of the orders will be revealed by the pharmacy at the conclusion of the study.

Blinding:

This is a double-blinded study. The ACTRI nurses, research technicians, participants and investigators will be blinded to the study material until after the statistical analysis is performed. Subjects will be blinded to study material by being injected by the nurses. Oxytocin and saline are both clear fluids and will be administered in Identical syringes. The study coordinator will submit a prescription to the pharmacy for the correct session day.

Pharmacists will deliver the study drug in a blinded fashion, and the doctor or nurse will subsequently administer the study drug to the subject keeping the doctor/nurse, subject, coordinator, and research assistants blinded until trial completion.

Timeline

To ensure drug clearance, Sessions 1 and 2 (OT; saline placebo or saline placebo; OT) will be separated by more than two days according to the participant and experimenters' availability[19,26]. After providing written consent (active enrollment), subjects will have 4 months to complete Sessions 1-2. Sessions will be offered to healthy volunteers until our sample size of 20 healthy volunteers has been reached. These sessions will be filled on a first-come-first-served basis.

1-2 years will be required for recruitment, data collection, and analysis.

Endpoints:

Primary Endpoint: When all data for the primary and secondary outcomes are collected and statistical analyses of these data are complete.

Outcome Measure(s)

Primary Outcomes:

- Pleasantness ratings of slow (primary) and fast gentle brushing
- Pain perception assessed in response to noxious pinprick (primary), pressure, and heat stimulation.
- Pain intensity and (un)pleasantness will be assessed with visual analog scales (VAS) as follows: pain intensity [anchors "no pain" (far left) to "most intense pain imaginable" (far right)] and (un)pleasantness ["extremely unpleasant" (far left) to "neutral" (middle) to "extremely pleasant" (far right)]. 100-point VAS scales are common, validated, and reliable measures of pain[74,75,76].

Key Secondary Outcomes:

All questionnaires will be administered using the Research Electronic Data Capture (REDCap) platform facilitated by study personnel, before or during Session 1. They include the following:

- State-Trait Anxiety Inventory (STAI; a measure of both state and trait anxiety[68])
- Pain Anxiety Symptoms Scale short form (PASS-20; an assessment of fear of pain[69,70])
- Multidimensional Assessment of Interoceptive Awareness (MAIA-2[71]; a measure of interoceptive sensibility)
- The Body Awareness Questionnaire (BAQ; a measure of attention to bodily processes[72,73])
- Autism Quotient (AQ[27]; observed to negatively correlate with baseline OT concentrations[23]).
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Sample Size Determination & Power

We expect that pleasantness ratings of C-LTMR-optimal touch will be significantly increased after local OT injection and that pain perception will be reduced. In published studies, differences in postsurgical pain after local infiltration with OT versus control resulted in very large mean differences in VAS pain ratings of Cohen's d = 3 to 4.5. In spinal nerve ligation (SNL) model rats, interplantar injection of OT versus control resulted in mean differences in paw withdrawal threshold of Cohen's d =13.8[19]. In addition, intranasal oxytocin (24IU) increases pleasantness of touch stimuli (especially driven by negative stimuli), with an estimated Cohen's d of ~3[23]. Although these are very large effect sizes, accounting for sampling variability and differences in proposed study design (acute pain; healthy adults; subcutaneous OT administration), we powered the study to detect a large effect size of d = 0.8. Assuming a within-subject correlation of 0.5 and an attrition rate of 25%,

the proposed sample size of $N = 20$ will provide 0.8 power to detect an effect size as small as $d = 0.8$ based on a two-sided $\alpha = 0.05$.

Data Analyses and Interpretation

General Statistical Approaches. Data will be analyzed descriptively and analytically. Descriptive statistics (means and standard deviations for continuous and proportions/counts for categorical outcomes) will be used to describe outcomes at baseline. Weighted generalized estimating equations (WGEE) will be employed, with appropriate link functions depending on the type of the response (e.g., identity for continuous and logit for binary outcome), to examine longitudinal changes in an outcome and longitudinal association between outcomes in regression analysis, controlling for covariates for Aims 1-2[123]. Unlike parametric models such as generalized linear mixed-effects models (GLMM), the semi-parametric WGEE requires no distribution assumption and yields valid inference for a broader class of data distribution under the missing at random mechanism[123]. WGEE provides valid inferences under the missing at random (MAR) mechanism[124]. We will use WGEE to test the missing completely at random (MCAR) assumption and will use the generalized estimating equations (GEE), if the MCAR is not rejected. GEE involves fewer parameters and provides more efficient inference than WGEE. Given the small sample size for Aims 1-2, we will complement the usual asymptotic inference with clustered bootstrap to improve inference validity and report the bootstrap inference if it differs from its asymptotic counterpart[125]. We set $\alpha=0.05$ for all analyses and use Holm-Bonferroni adjustments for <= 5 tests[126] and False Discovery Rate (FDR) for > 5 tests[127]. When correlated outcomes are analyzed (e.g., outcomes in related domains), corrections will be calculated based on the effective number of independent tests that account for correlations between the outcomes[128]. Whenever possible, effect size will be reported in addition to point and interval estimates. All analyses will be performed using the latest versions of R[129] and SAS[130]. Hypothesis Testing. For Aim 1, separately for OT and saline placebo sessions, we will compare changes in ratings of pain over time between the OT and control arm using WGEE, where time (one binary indicator) will be the predictor, controlling for covariates. A significant time effect, tested using appropriate linear contrasts, will support the hypothesis that the OT injection has effects on the outcome. We will follow with *post hoc* analyses to estimate the effect size of the OT injection. For Aim 2, we will apply the same approach in Aim 1 to pleasant touch outcome. Age and race/ethnicity will be included as potential covariates in all analyses.

10. HUMAN SUBJECTS

Subject Population

A total of 20 healthy adults, ages 18-65, will complete two separate test sessions in a within-subject crossover study. Equal numbers of males and females will be recruited. Data will be analyzed to determine if sex is a significant predictor of study outcomes. 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
3) Healthy

Exclusion Criteria:

4) Body-mass index under 20
5) Sensory or motor nerve deficit
6) Acute or chronic pain
7) 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).
8) Any disease, diagnosis, or condition (medical or surgical) that, in the opinion of the Principal Investigator, would place the subject at increased risk (active gynecologic disease in which increased

tone would be detrimental e.g., uterine fibroids with ongoing bleeding), compromise the subject's compliance with study procedures, or compromise the quality of the data
9) Unstable psychiatric conditions
10) Needle phobia, needle-related anxiety, or history of fainting from needles
11) Current use of opiate medication(s)
12) Hypersensitivity, allergy, or significant reaction to any ingredient of Pitocin®
13) Currently pregnant or pregnant within the last two years
14) Currently nursing or lactating
15) Current or history of ventricular tachycardia, atrial fibrillation or prolonged QT interval
16) Past or current history of hyponatremia or at risk for hyponatremia
17) Current use of pseudoephedrine, thiazide diuretics, loop diuretics, combination diuretics, lithium, carbamazepine, enalapril, Ramipril, celecoxib, temazepam, gliclazide, glimepiride, glibenclamide, glipizide, omeprazole, pantoprazole, desmopressin, SSRI's, MAOI, or the recreational drug ecstasy
18) Latex allergy

Participants will be asked to avoid drinking alcohol for at least 48 hours prior to study sessions, avoid over-the-counter pain medications and other over-the-counter medications, including allergy medications for 24 hours, avoid exercise, or drinking more than 1 caffeinated drink for 24hrs, and avoid nicotine andcaffeinefor 2hrs before study sessions. We will collect information about these behaviors at each study session to include as study covariates but will not exclude for these additional behaviors. There will be no other restrictions on medication(s) during this study. They will be permitted to use any supplements, complementary and alternative therapies, treatments, and/or procedures for medical purposes during the course of this study.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Subjects will be recruited through three primary streams: (1) from IRB approved flyers and ads posted in the San Diego area, 2) the ResearchMatch website and 3) from past studies at UCSD. We will begin study recruitment after we have completed all NIH oversight requirements.

1) We may post IRB approved flyers throughout the community.

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) The study may be advertised to participants from our lab's past studies at UCSD.

We will not 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. 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. 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. 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 directly before informed consent is obtained when screening criteria are readministered reviewed. 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. Only subjects who have consented 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. 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. 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.

Recruitment materials that are not included in this submission (such as researchmatch ad) will be submitted to and approved by the IRB prior to use.

12. INFORMED CONSENT

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 provide written consent, using an IRB-approved consent form during their first study session. The consent process will take place prior to performing any study related procedures and in a private room with the door closed. The study team member will describe the study, including detailed information about risks and benefits, to potential subjects. The study team member will provide potential subjects with an IRB-approved consent form. Potential subjects will be given ample time to read this consent form at the same visit or may take it with them to read 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 signing the consent form. As this research is subject to HIPAA privacy rule provisions, subjects will also be requested to sign a separate HIPAA authorization for the use of protected health information.

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 signed consents will be maintained on laboratory password protected computers and servers, as well as in marked binders secured in locked filing cabinets within private offices or cubicles in Dr. Case or Dr. Zeidan's laboratories in 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 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 for heart rate recording (ECG):
The ECG procedure may cause some mild discomfort during the placement and removal of the leads to and from the skin. You may also experience some local irritation, redness, or burning in the areas where the leads are attached.

Risks and discomforts associated with Oxytocin:
We do not expect any risks from OT injected in the skin beyond possible headache, facial flushing, and sensation of heart pounding. Skin injection of OT has been conducted in only one published human study. In this study subcutaneous injection of 4 µg/4 ml OT just prior to surgical incision resulted in more stable hemodynamic parameters during surgery and reduced postsurgical pain. Adverse events were not systematically addressed in this paper, however no gross problems were reported.

Other routes of peripheral and systemic OT administration have demonstrated safety in healthy volunteers. Most clinical reports of intranasal oxytocin fail to mention adverse events or state that no serious or severe adverse events were noted. A few reports provide more detail, including a study of 49 older men (age 73 years; range 65-78) which observed no serious adverse events and no difference between 41µg intranasal OT and placebo [28], and a pediatric study [29] and meta-analysis showing no safety signals with prolonged intranasal oxytocin administration for weeks [30].

For intramuscular (IM) injection of oxytocin, only 1 study has been conducted in non-pregnant/postpartum persons; in these healthy participants, IM injection of 10IU (~17 µg) oxytocin (EVER Neuro Pharma GmbH, Unterach, Austria) in the thigh did not cause any serious adverse events or clinically significant findings for any safety parameters[31]. OT produces no tissue toxicity in these concentrations when injected intravascularly or into the muscle. Based on preliminary studies with intravenous and intranasal administration of oxytocin from the lab of James Eisenach at Wake Forest University, particularly at plasma oxytocin concentrations > 350 pg/ml, the following adverse events may occur: headache; facial flushing; sensation of heart pounding.

IV and IM OT (10IU) are frequently given for labor augmentation and postpartum hemorrhage. Based on long and widespread use in obstetrics, the following risks and side effects have been reported from intravenous and intranasal injection of oxytocin within the dosage recommendations to pregnant and immediate postpartum women: anaphylactic reaction; cardiac arrhythmia; fatal afibrinogenemia; nausea and vomiting; premature ventricular contractions; subarachnoid hemorrhage; hypertensive episodes; postpartum hemorrhage; pelvic hematoma; rupture of the uterus; severe water intoxication with convulsions, coma, or death with a slow oxytocin infusion over a 24-hr period. Because the dose of oxytocin we will be injecting is far lower than the 10IU dose administered to pregnant and postpartum women[28] and the ~24IU dose administered intranasally for research purposes[23], we do not expect any of the above side effects to occur. Of course, given the effects of OT on pregnancy, we will exclude all pregnant persons to eliminate reproductive risk.

Risks and discomforts associated with subcutaneous injection:
The main risks of a subcutaneous injection are pain, redness, swelling, itchiness, bruising, or irritation around the site of injection for 1-2 days after injection. Rare complications include infection of the puncture or accidental injection into a blood vessel or nerve This is not expected to increase risk given the demonstrated safety of larger doses of intravenous OT described above.

Risks and discomforts associated with blood draw (funds permitting for baseline OT assay):
The main risks of drawing blood from a vein include discomfort at the site of puncture, possible bruising and swelling around the puncture site, and (rarely) an infection or faintness from the procedure. Some subjects

could experience a vasovagal (fainting) response due to the discomfort of needle insertion or anxiety associated with the procedure.

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 sensory stimuli:
Mechanical and pressure pain stimuli may be slightly uncomfortable or cause brief skin irritation. Stimuli will not break or damage the skin. There are no known risks of the gentle brushing although some participants could experience it as uncomfortable.

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. 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.

Screening and questionnaires:
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.

Heart rate recording (ECG):
ECG leads will be removed gently and skin will be examined before and after to ensure absence of any irritation.

Oxytocin:
All participants will be screened to ensure they are not pregnant (including urine pregnancy test for those capable of pregnancy) and do not have any medical counterindications to receiving oxytocin. These participants will also be asked to either abstain from sexual intercourse or use a reliable, effective contraception during the study. The study dose is 10x smaller than doses typically administered intranasally of ~24IU[23] or 41 µg (also about 24IU) [28], and almost 5x smaller than those given intramuscularly or intravenously

for labor augmentation (10IU)[32]. In addition, blood pressure and oxygenation will be monitored regularly after OT injection.

Subcutaneous injection:
The injection site will be cleaned using sterile technique. 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.

Blood draw:
The risks of discomfort, bruising, and swelling around the puncture site are common while the risks of infection and fainting are rare. The risk of fainting will be reduced by observing subjects during and following venipuncture to ensure that they feel comfortable rising from their seated position. Subjects with a history of vasovagal responses will be excluded.

Heat and 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. If subjects want to stop pain stimulation, they may remove their limb for the test apparatus and ask to stop, and may be dismissed.

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 the pregnancy tests will be shared with the subject by a medical provider affiliated with the study and appropriate referrals for follow-up care will be made.

Monitoring:

This study will follow the Data and Safety Monitoring Plan prepared for NIH:
Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

The DSMP outlined below will provide appropriate oversight and monitoring to ensure the safety of participants, the validity of the data, and make intermittent recommendations whether to continue, modify or stop the study. The DSMP will utilize an independent DSMB to ensure the effective institution of the DSMP.

This DSMB will have discretion to unblind any results, or conduct any inquiry needed to ensure the safety and efficacy of the trial at the request of the DSMB chair. The committee will maintain a written record of its meetings.

Scope of Data Monitoring
The primary source of the data will be adverse event reporting.

Study admission data
Monitoring of admission data will include the number of subjects requesting participation in the study, number of subjects screened and number of subjects admitted to the study. The DSMB may request a report of the reason why subjects were disqualified from participating in the study. For subjects admitted to the study, the DSMB will review eligibility criteria for admitted subject, any protocol deviations and/or violations, and the demographic distribution of the subjects by group.

Protocol Compliance
The DSMB will monitor the data to assess compliance with the protocols including the adherence to the randomization schedule. The DSMB will also monitor the quality and completeness of the data being collected, including the frequency of missing or erroneous data, and presence and frequency of outliers.

Safety Data
Monitoring of safety data will include review of Adverse Events (AEs) and Serious Adverse Events (SAEs), trial retention, and reason for drop out. Safety information will be reported to the DSMB in an unblinded manner. Formal statistical analyses of the safety data may be requested by the DSMB. For SAEs, data will include all the adverse event data meeting the FDA definition of serious adverse events. In the assessment of SAEs, the DSMB will review each individual case including treatment group assignment. After each meeting of the DSMB, the secretary will forward a summary report of all serious and unexpected adverse experiences to the principal investigator to summarize the DSMB's review of the serious and unexpected adverse events reported. Furthermore, the DSMB will make a recommendation to continue, modify or halt the study protocol. This report will be transmitted to the UC San Diego IRB and NIH. Safety data will be prepared for review following the enrollment of each 10 subjects.

Establishing a DSMB Board membership
The DSMB will be appointed by Dr. Case and Dr. Said with the purpose of reviewing, approval, and monitoring the implementation of the DSMP. The DSMB will have two members encompassing multidisciplinary expertise who are not involved in the study protocol. Board members will have no financial and/or scientific ties to the outcome of the clinical trials to avoid any real or perceived conflict of interest. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data.

Board meeting schedule
The board will have scheduled meetings twice a year and expedited meetings to review unexpected SAEs or other urgent issues that may arise during the trial. Unscheduled meetings may be initiated by the DSMB chair, Dr. Case, or Dr. Said. The data to be reviewed by the DSMB will be available to the Board members.

DSMB Recommendations:
DSMB recommendations will be made in writing by The DSMB chair to Dr. Case. DSMB recommendations will then be forwarded to the NIH program officer and UC San Diego IRB.

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:

- Related (Possible, Probable, Definite)
    - The event is known to occur with the study intervention.
    - There is a temporal relationship between the intervention and event onset.
    - The event abates when the intervention is discontinued.
    - The event reappears upon a re-challenge with the intervention.
- Not Related (Unlikely, Not Related)
    - There is no temporal relationship between the intervention and event onset.
    - 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:

- Mild: no intervention required; no impact on activities of daily living (ADL)
- Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
- 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 NIH 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 NIH within 14 days of the investigator becoming aware of the problem.

Adverse Event Reporting for IND Studies:
SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitors(s), IRB, FDA, and NIH in accordance with requirements. For the IND:

- 7-day IND Safety Report (unexpected fatal or life-threatening AEs related to the intervention); a copy of the report sent to the FDA will be submitted to the NIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to the intervention); a copy of the report submitted to the FDA will be submitted to the NIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.
- All other AEs documented during the course of the trial will be reported to NIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NIH 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 affective touch and pain perception, with potential applications for 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 mechanisms of pain and touch perception.

19. EXPENSE TO PARTICIPANT

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

20. COMPENSATION FOR PARTICIPATION

Participants will receive $80 for the Baseline session, $60 for Session 2, for a total of $140. A free parking voucher code will be made available for each study session.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

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

Dr. Laura Case, PhD— 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. Engy T. Said, MD— Co-Investigator

- Role/ Responsibilities:
- Oversees all study members, procedures, information, and research activities.
- Consulting study physician
- Qualifications/Certifications/Licenses:
- CITI Training in Biomedical Research and Good Clinical Practice
- Board-certified anesthesiologist with fellowship training in regional anesthesia and acute pain. Dr. Said holds a license to practice medicine in California, has medical privileges at the UC Medical Centers, and will be responsible for the overall management of this study.

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

- Role/Responsibilities:
  - Consulting study physician
- 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. Hemal Patel, PhD – Co-Investigator

- Role/Responsibilities:
  - Conduct ELISA assays for oxytocin
- Qualifications/Certifications/Licenses:
  - Professor, Dept of Anesthesiology
  - Will not interact with human subjects

Dr. Benedetta Albinni, PhD – 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, 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

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, 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
  - BA in Psychology

Michael Haupt, UCSD Graduate Student in Cognitive Science – 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, 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

Benjamin Goldstein, UCSD Medical Student

- Roles/Responsibilities: Mr. Goldstein 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, randomization, scheduling, and acting as a communication point for the study. He will help maintain site regulatory 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
    - Current Medical student

Jacob Ross, UCSD student in Neurobiology – Research Volunteer

- Roles/Responsibilities: Mr. Ross 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, 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 Neurobiology

Leyla Ozdoyuran, UCSD student in Clinical Psychology – Research Volunteer

- Roles/Responsibilities: Ms. Ozdoyuran 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, 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 Clinical Psychology in progress

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

Registered Nurses in the ACTRI may administer subcutaneous injections.

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23. FUNDING SUPPORT FOR THIS STUDY

An ACTRI Pilot Award application has been submitted for funding consideration.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

An IND application (sponsor Laura Case PhD) has been submitted to the FDA for subcutaneous injection of oxytocin for research purposes. An investigational drug fact sheet is appended.

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.