Protocol Title: Sensory and Opioid Mechanisms of Affective Touch
Abbreviated Title: Affective Touch
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Principal Investigator

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Human Research Protections Program Investigator and Staff Training:

For this protocol, the following "Just in time" human subjects protection training courses are required for investigators and staff:
None

Total requested accrual
30 Healthy Volunteers

Project Uses Ionizing Radiation:	☒ No	☐ Yes
IND/IDE	☒ No	☐Yes
Durable Power of Attorney	☒ No	☐ Yes
Multi-institutional Project	☒ No	☐ Yes
Data and Safety Monitoring Board	☒ No	☐ Yes
Technology Transfer Agreement	☒ No	☐ Yes
Samples are being stored	☒ No	☐ Yes

Flesch-Kincaid reading level of consent form: 8.3

Précis:

Objective: Our recent pilot study found evidence suggesting that blocking endogenous opioid release increases the pleasantness associated with having the skin stroked. Deep pressure touch (observed in hugs and massage) also typically conveys a sense of pleasantness. This increased pleasantness contrasts with evidence that blocking endogenous opioid release increases pain. The current study will examine the role of endogenous opioids in the pleasantness of light skin stroking and deep pressure touch, and contrast it with their role in the unpleasantness of a painful heat stimulus. Further, it will examine the neural basis of observed perceptual changes, using fMRI. This study constitutes the first study of the K99 phase of a K99/R00 grant application recently submitted to NCCIH by Dr. Laura Case.

Study Population: 30 healthy participants will be enrolled in the study.

Design: Participants will receive intravenous saline or intravenous naloxone on separate days to investigate the effect of mu-opioid antagonism on the intensity and pleasantness of superficial and deep affective touch and the intensity and unpleasantness of cutaneous heat pain. Using a double-blind cross-over design, functional Magnetic Resonance Imaging (fMRI) will be conducted during sensory testing before and after the infusion of each drug to examine the neural mediation of opioid effects on touch perception. Ratings of mood, anxiety, pain intensity, pleasantness/unpleasantness, wanting and liking will also be collected throughout the study session.

Outcome measures: We will compare subjective ratings (mood, calmness, anxiety, pleasantness, wanting, liking, pain intensity and unpleasantness) during naloxone and saline to: 1) Determine whether naloxone increases the pleasantness and/or intensity of affective touch (light brush and deep compression); 2) Determine whether naloxone increases the unpleasantness and/or intensity of cutaneous heat pain; 3) Determine the role of mood or anxiety changes in mediating the effect of endogenous opioids on these perceptual measures; 3) Determine changes in the brain activation related to these effects.

Precis posted online at clinicaltrials.gov: see Attachment 3

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List of Abbreviations

PANAS = Positive and Negative Affect Schedule
fMRI = Functional Magnetic Resonance Imaging
C-LTMR = C Low Threshold Mechanoreceptors
MRI = Magnetic Resonance Imaging
MDMA = Methylenedioxymethamphetamine
LSD = Lysergic acid diethylamide
MINI = Mini-International Neuropsychiatric Interview
NSAIDs = Nonsteroidal anti-inflammatory drugs
CRIS = Clinical Research Information System
CC= Clinical Center
FMRIF = Functional MRI Facility
NRS = Numeric ratings scale
LIP = Licensed independent practitioner
EPI= echo planar imaging
BOLD= blood oxygenation level-dependent
MP-RAGE = Magnetization Prepared Rapid Acquisition by Gradient Echo
TCI = Temperament and Character Inventory
BAS = Behavior Appetitive System Scale
HADS = Hospital Anxiety and Depression Scale
NEO (personality inventory)
GDS = Genomic Data Sharing
DoH = Declaration of Helsinki
FWA= Federal wide Assurance
CNS = Central Nervous System
SPSS = Statistical Package for the Social Sciences
FSL = FMRIB Software Library
AFNI = Analysis of Functional NeuroImages

1. Introduction and Background

A better understanding of the human endogenous opioid system and its innate activation mechanisms is important for unraveling the neurochemical underpinnings of alternative therapies for depression, anxiety and pain. Here, we investigate the role of endogenous opioids in affective dimensions of touch and pain with the hypothesis that this system modulates the pleasantness of touch and the unpleasantness of pain.

Since brain regions rich in opioid receptors, such as the insula, cingulate cortex and orbitofrontal [1], are activated by a subtype of unmyelinated sensory afferents (C low-threshold mechanoreceptor; C-LTMR) which respond particularly well to slow gentle stroking of the skin

and that this type of touch is perceptually pleasant ([2, 3]), it is likely that endogenous opioids are released by this stimulus. Primate studies have previously shown that monkeys both solicit and receive more grooming after opioid blockade ([4]; [5]; [6]; [7]; [8]), suggesting an increased wanting or liking of social touch under reduced opioid levels. Similarly, in humans, we have some preliminary evidence that pleasantness ratings of gentle skin stroking increase after opioid blockade by naloxone [9], suggesting that reduced opioid levels actually make touch more pleasant and desirable. However, it is not clear whether the perceptual effect of blocking endogenous opioids is due to a direct effect of opioids on the sensory pathways or is an indirect effect caused by the opioids modulating mood and mood in turn modulating touch perception [10]. The possibility of the indirect effect is supported by data showing that opioid blockade leads to a negative mood state [11]; [12]; [13]. One theoretical hypothesis is that a negative mood state increases the hedonic value of social touch [10].

A parallel system to the skin's C-LTMRs may be present in form of unmyelinated pressure-sensitive afferents identified in skeletal muscle and tendon of cat [14] which may mediate the pleasurable experience of deep pressure touch. In humans, deep pressure touch has been shown to reduce anxiety [15], pain and unpleasant affect [16]. For the beneficial effects of massage therapy [17], the exertion of moderate pressure (compared to light pressure or vibration) is necessary and leads to greater reduction of stress and anxiety as well as higher pleasantness ratings [18]. Both light skin stroking and deep pressure touch are components of numerous complementary health techniques which significantly reduce depression, stress, and pain [19, 20]. By including deep pressure touch as a condition in our current study we aim to investigate, through blockage of the endogenous opioid system (naloxone administration), if the pleasantness of light skin stroking and the pleasantness of deep pressure touch are both similarly dependent on endogenous opioids, and whether mood mediates this effect.

Endogenous opioids are central to the perception of pleasure and reward (wanting and liking) which serve as crucial balancing systems for pain and associated psychiatric conditions. To address the question of pain modulatory properties of the endogenous opioid system, specifically on the affective component of pain, we include an experimental heat pain condition in our study and administer an opioid blockade (naloxone). Previous studies of the effect of blocking opioid

receptors on pain perception have produced conflicting results: no effect on pain [21-24], increased pain following high dose and decreased pain at low dose naloxone[25-28]. The same contradictory findings are true for several rodent studies [29-32]. To our knowledge, the ratings in the human studies were all unitary measures of pain intensity. However, a more recent study on this topic [33] utilized rating systems for both pain unpleasantness and pain intensity allowing the authors to differentiate the affective component of pain. The opioid blockade significantly increased pain unpleasantness ratings of experimental pain but the pain intensity ratings remained unaffected [33]. Our aim is to replicate this finding and add to it brain imaging data (fMRI) to characterize the brain areas associated with producing this dichotomized pain perception. By deciphering this neuronal process we could potentially also understand how mood can alter pain unpleasantness independent of pain intensity [34], if understood these components strengthen therapeutic strategies for treatment of chronic pain using mood altering therapies.

2. Study Objectives

Hypothesis 1 (primary outcome): Participants will experience a significant increase in the pleasantness but not intensity of cutaneous brushing and deep skin/muscle pressure after administration of naloxone (compared to saline).

Hypothesis 2 (secondary outcome): Participants will experience a significant increase in the unpleasantness but not intensity of cutaneous heat pain after naloxone administration.

Hypothesis 3 (secondary outcome): The effect of endogenous opioids on perception will be partially mediated by changes in mood, with negative mood increasing the pleasantness of pleasant touch and increasing the unpleasantness of pain.

Hypothesis 4 (secondary outcome): Stimulus-evoked neural activations will be modulated by naloxone administration, with preferential effects in cingulate cortex and insula.

3. Subjects

a. Description of study populations

Based on our power calculations, we would like to have 24 healthy men and women who meet the inclusion/exclusion criteria described below participate in the study. Because of possible dropouts during the study, we will set our maximum accrual at 30 participants (see detailed explanation of sample size estimate on p. 23). Withdrawals/dropouts will be replaced. In accordance with HRPP SOP 14F and provided they are not subordinates, relatives, or co-workers of the investigators, or NCCIH DIR employees, NIH employees may participate in this study.

b. Inclusion criteria

All subjects must be:

1. Between 18 and 50 years old.
2. Right-handed (on Edinburgh Handedness Inventory [53]).
3. Fluent in English.
4. Able to provide written informed consent.

c. Exclusion criteria

Overall exclusion criteria for the study

1. Unable to comply with study procedures (or does not rate stimuli as tolerable) or unable to schedule visits promptly (including inability to schedule the second session within approximately 14 days of the first session)
2. Pregnancy or breastfeeding.
3. Use of recreational drugs in the past month (e.g., marijuana, MDMA [“ecstasy” or “molly”], LSD, cocaine, methamphetamine, heroin, prescription and/or opioids).
4. Congenital lower limb deficiency or amputation.
5. Peripheral neuropathy, dermatological condition such as scars or burns, or has had a tattoo in the testing region within the previous four weeks that might influence cutaneous sensibility.

6. Women who consume more than 7 alcoholic beverages per week, and men who consume more than 14 drinks per week.
7. Current chronic pain condition or has had chronic pain in the past year (painful condition lasting more than six months), including ongoing treatment with medications for neuropathic pain (e.g. gabapentin, tricyclic antidepressants, pregabalin, tramadol)
8. Major medical condition, such as kidney, liver, cardiovascular (including blood clots, hypertension, preexisting cardiac arrhythmia), autonomic, pulmonary, or neurological problems (e.g., seizure disorder) or a chronic systemic disease (e.g., diabetes).
9. Current diagnosis or pharmacological treatment of psychiatric disorders such as major depression, major anxiety-related problems, post-traumatic stress syndrome, bipolar disorder, psychosis, attention-deficit/hyperactivity disorder or current or lifetime alcohol or substance abuse disorders (as identified in study #16-AT-0077)
10. Participant has metal in his/her body which would make having an MRI scan unsafe, such as pacemakers, medication pumps, aneurysm clips, metallic prostheses (including metal pins and rods, heart valves or cochlear implants), shrapnel fragments, permanent eye liner or small metal fragments in the eye that welders and other metal workers may have.
11. Participant is uncomfortable in small closed spaces (has claustrophobia) so that he/she would feel uncomfortable in the MRI machine or cannot lie comfortably flat on his/her back for up to 75 minutes in the MRI scanner.
12. Participants weighs more than 550 lbs.
13. Participant has taken any pain medication other than an over-the-counter NSAIDs or acetaminophen within the last month or for more than one month on a continual basis within last six months.
14. Previous participation in 13-AT-0143 (related study).
15. NIH employees who are subordinates, relatives, or co-workers of the investigators, or NCCIH DIR employees.
16. Participants using medications that play into opioid pathways (e.g. loperamide or dextromethorphan), that could potentially interact with naloxone (naltrexone, methylnaltrexone, droperidol, fenfluramine and clonidine)

17. Participant using any herbal supplements (such as yohimbine) due to risk of unknown dangerous interaction as there is no data for herbal preparations and naloxone.
18. Participant has allergies to naloxone or similar drugs.

Exclusion criteria for individual study session

1. Has consumed alcohol within 24 hours, shows signs of alcohol withdrawal syndrome, or has behavioral signs of intoxication will be excluded immediately and not have the possibility to reschedule their session.
2. Used topical pain-relieving creams in the testing area (e.g. methylsalicylate, capsaicin) within 24 hours of testing or used non-steroidal anti-inflammatory drugs (NSAIDS, e.g. aspirin, ibuprofen), acetaminophen, or naproxen within 3 days of testing. *

* To be determined during the pre-session screening (see Attachment 2: Pre-Session Screening). Participants who cannot refrain from these activities may have their session rescheduled up to two times. If the participant is found non-compliant during the second rescheduled appointment, he or she will be excluded from the study.

An Eligibility Checklist can be found in Attachment 2.

4. Study Design and Methods

a. Study overview

Healthy male and female volunteers will be recruited and informed that they may be eligible to participate in a study that examines the role of endogenous opioids in processing several types of touch. We will explain that participants will receive saline and naloxone on two different days with a minimum 24 hour wash-out period between testing sessions to minimize the possibility of carry-over effects, serum half-life for naloxone ranges from 30 to 81 minutes. The drugs will be administered in association with different types of touch stimuli on the calf of the leg including light brush stroking of the skin, compression around the limb, and application of heat to the skin, including moderately painful heat. Functional magnetic resonance imaging (fMRI) will be conducted simultaneously to observe the effect of the drug infusions on touch processing. The

purpose of the study is to identify the role of endogenous opioids in perception of light and deep pressure touch as well as experimental pain.

A pre-screening telephone call will be conducted to determine eligibility. If eligibility requirements are met, subjects will be scheduled for the test sessions. Screening will be accomplished under NCCIH protocol 16-AT-0077 ("Clinical and Scientific Assessment of Pain and Painful Disorders"). If deemed eligible, the participant will provide consent for the current protocol prior to performing any procedures specific to this protocol. Consent may occur during an additional, separate visit from the subsequent two research sessions. See Figure 1 for Study Flow. All visits will be on an outpatient basis and all experiments will be conducted in Building 10 of the NIH.

All subjects will be informed about naloxone, including its pharmacological properties, clinical use, and possible side effects. Subjects will also be informed that they may withdraw from participation at any time during the course of the study and that they will be compensated for each portion of the study that they have completed.

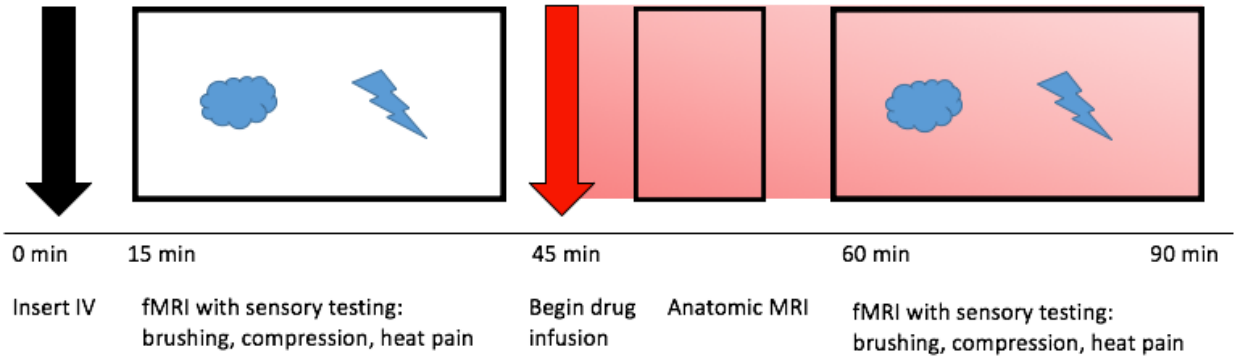

Figure 1. Study Flow. Each MRI session will follow the timeline shown.

b. Recruitment

We anticipate recruiting up to 30 potential participants. Participants may be recruited from a currently active NCCIH Phenotyping protocol (16-AT-0077). Participants may also be recruited from the NIH Clinical Trial recruiting line (1-800-411-1222). When a potential subject contacts us, he or she will be scheduled for a telephone pre-screening session (described below). Cold-calling will not be used to contact or recruit potential participants. NIH employees will not be directly recruited by or through their supervisors to participate in this study. NCCIH employees cannot participate in this protocol.

Telephone Interview (pre-screening)

Each potential participant will undergo a telephone pre-screening interview of approximately 15 minutes (see Attachment 1 for details). During the telephone interview, the subject will be informed about the general procedures of the study, and inclusion/exclusion criteria will be assessed. If the potential subject does not meet these criteria, the interview will be terminated and screening information will be destroyed. However, if the potential participant agrees, we will retain their contact information to contact them later about other studies in the lab for which they may be eligible (including name, email, and phone number). Potentially eligible subjects will be told that to serve as participants they will be required to undergo a drug screening and, for participants who can become pregnant, a pregnancy test. If the potential subject agrees to continue to participate, they will be scheduled for their first session. Further screening information will be drawn from previous participation in the NCCIH Phenotyping Protocol, 16-AT-0077. Participants will be informed of this.

c. Screening

Screening

Screening for this protocol is done under NCCIH protocol 16-AT-0077 (“Clinical and Scientific Assessment of Pain and Painful Disorders”). Screening will be done within a year of participation in this protocol and data required includes clinical MRI, medical exam, psychological interview, sensory testing and the Edinburgh Handedness Inventory. If deemed eligible, the participant will

provide consent for the current protocol prior to performing any procedures specific to this protocol.

Once enrolled in T-AT-0285, a LHP will review eligibility criteria at the beginning of each session, and confirm that participants are eligible and meet pre-session criteria.

d. Study procedures

Consent will be obtained before any study procedures will be done. Upon arrival at the Clinical Center, the participant will be assigned a CRIS identification number through the NIH Admissions Office. The consent form will be explained and all questions will be answered before the participant is asked to sign the consent form (see Section 14 for details). Consent may occur during an additional, separate visit from the subsequent two research sessions.

Participants eligible to proceed will be asked to undergo two testing sessions, separated by at least 1 day, in the NIH Clinical Research Center's Functional MRI Facility (FMRIF, Building 10, Room B1D307 or B1D305). Each participant will receive naloxone on one day, and saline on the other, with drug order counterbalanced across subjects. At each visit, a urine sample will be collected from all participants for drug screening. In addition, at each visit, participants who are able to become pregnant will also take a urine pregnancy test. Date of onset for previous menstrual cycle will be documented to allow for later analysis of confounds of menstrual cycle in perceptual outcomes. Medical inclusion and exclusion criteria will be reviewed with the participant at the beginning of each study session to confirm continued eligibility. The participants will have their intravenous line placed before any part of the fMRI will start. A baseline scan including data collection for all sensory conditions will be collected before the intravenous infusion. Drug infusion will then start with a bolus injection followed by a continuous infusion of naloxone or saline and the full sensory paradigm will be repeated. An anatomical MRI will also be acquired.

Sensory testing paradigm

Sensory testing will occur on the participant's left lower leg. While it is most common for brushing paradigms to brush on the hairy skin on the arm (C-LTMR fibers primarily innervate

hairy skin), several studies have reported the same preference for slow, C-LTMR brushing on the leg [35], including the shin [36]. According to our unpublished data the calf is also a site of high pleasantness ratings for deep compression, and more accessible in the MRI scanner. We will therefore conduct all sensory testing on subjects' lower leg. Participants will be asked to wear shorts or change into scrubs for each session in order to access the lower leg.
During each period of fMRI recording (before and after drug infusion) we will administer six stimulus blocks (approx.5 min each). Each block will contain only one type of stimulus (fast or slow brushing, high or low pressure, high or low heat), with stimuli lasting 10-30 sec and inter-stimulus-intervals of at least 15 sec. Gentle brushing will be performed at two speeds (~3cm/s and ~30 cm/s) using a soft brush. A trained experimenter blind to the drug condition will administer the brushing, using audio or visual cues to keep the correct rate of brushing. Since the subject will be in the MRI scanner throughout all stimulation, the experimenter will not be visible to the subjects, thus eliminating interpersonal cues. Deep pressure will be administered using an inflatable compression cuff designed by the NIH Clinical Center machine shop. Similar to a blood pressure cuff, the inflatable cuff will wrap around the participant's lower leg and will inflate to a pleasant pressure and a less pleasant pressure (both less than 120 mmHg). Heat stimuli will be administered by the trained experimenter using a contact thermode (Medoc Pathway System; Medoc Ltd., Advanced Medical System, Israel). Heat will be approximately 46^{o}C (painful) and approximately 41^{o}C (non-painful). Similar painful heat stimuli have been used in our lab and elsewhere, including in approved NIH protocols [37].

After each stimulus block, subjects will provide ratings of pain intensity, unpleasantness/pleasantness, bad mood/ good mood, anxiety/calm, wanting and liking (see below and Attachment 2). We will use stimulus presentation software such as e-prime or matlab for stimulus presentation and recording of ratings. NRS ratings of current ongoing pain and discomfort will be taken after functional MRI scans.

Drug Administration

All study participants will receive both drug conditions (naloxone and saline), one at each experimental session. Both substances will be administered intravenously by licensed providers. For naloxone, to achieve a constant plasma level throughout the ~45 min testing phase, a bolus

dose of naloxone (0.05 mg/kg bodyweight; generic) will administered as a manual injection, via an intravenous line, followed by a pump administered intravenous infusion of 0.08 mg/kg/h starting immediately after the bolus injection and continuing for the duration of the scan. A maximum dose of 10mg naloxone will be administered, which is the maximum dose used clinically to reverse the effects of opiates (Micromedex). Individuals over 200lb will receive a slightly lower dose per body weight in order to not exceed the 10mg maximum. We have previously used this dosage and administration procedure for healthy subjects and fibromyalgia patients in Protocol 13-AT-0143. The saline will be administered in the same fashion, i.e. as a manual bolus injection followed by a pump administered infusion of saline, both using the same volume per individual as calculated for the naloxone bolus and infusion (based on body weight). All solutions will be prepared by the Clinical Center pharmacy and furnished to the investigators in individual subject doses on the day of the experiment for that subject. Respiration rate, blood oxygen saturation, heart rate and blood pressure will be monitored by a nurse or nurse LP during both infusions. The participants are under continuous visual monitoring when in the MRI-scanner via a camera. Participants will be equipped with a panic button to press in case of any subjective need to be immediately evacuated from the MRI scanner. A crash cart is available on site at all times and the MRI-scanner facilities are code team accessible. The procedure described above has been successfully used in healthy volunteers and fibromyalgia patients under similar circumstances, with no significant adverse effects (eg [38] [9]; NIH protocol 13-AT-1043). At the end of each session, subjects will be asked to rate naloxone-related adverse effects (dry mouth, dry skin, blurred vision, sedation, nausea, dizziness, headache) on a scale from 0=non-existent to 6=extremely strong. The administration of naloxone will be performed by a nurse practitioner or registered nurse in the Functional MRI Facility (FMRIF), and neither the experimenter nor the subjects will know which substance was administered on which day until after the study is complete. Participants will be observed for 60 minutes after the infusion has been discontinued (approx. one half-life of naloxone) to ensure that participants are not experiencing any adverse effects.

MRI Data Acquisition

Functional scan: Each participant will be scanned on a 3T MRI scanner using a standard head coil. During each session, two fMRI scans (containing multiple runs) will be collected using a blood oxygenation level-dependent (BOLD) protocol with a T2*-weighted gradient echo planar

imaging (EPI) sequence. During the functional scans heart rate, blood oxygenation, and respiration rate will be monitored. We will use a 3D MP-RAGE (Magnetization Prepared Rapid Acquisition by Gradient Echo) T1-weighted sequence for the anatomical scan. Including the functional and anatomical scan, subjects will be continuously in the scanner for approximately 75 min (see Figure1).

Visual Analogue Scales

Separate scales (see Attachment 3) will be used to assess sensory intensity/pain, unpleasantness/pleasantness, mood, and anxiety at baseline and throughout each session using a computer presentation method. Participants will use a mouse to log their ratings. Pain intensity will be assessed on a scale ranging from no sensation (-100) to pain threshold (0), to intolerable pain (100). Sensory hedonics (unpleasantness vs. pleasantness) will be assessed on a scale ranging from extremely unpleasant (-100) to neutral (0), to extremely pleasant (100). Mood will be assessed on a scale ranging from extremely bad mood (-100) to neutral mood (0), to extremely good mood (100), anxiety will be assessed on a scale ranging from extreme anxiety (-100) to neutral (0) to extreme calm (100), wanting will be assessed on a scale ranging from not at all (-100), to neutral (0), to very much (100) and liking will be assessed on a scale ranging from not at all (-100), to neutral (0), to very much (100). These scales have been used previously to separate the intensity and hedonic components of pain perception (eg.[39] [40]).

Questionnaires

Participants will fill out several questionnaires before or after the first test session: the Temperament and Character Inventory (TCI), which includes dopamine-related traits [41], the Behavior Appetitive System Scale (BAS) [42], the Hospital Anxiety and Depression Scale (HADS) to evaluate anxiety [43], the NEO Personality Inventory [44], and the Social Touch Scale [45]. If there is not sufficient time to complete all questionnaires during the first session, those questionnaires will be completed during another session of the study. At the end of each session participants will be asked whether they believe they received saline or naloxone that day.

e. End of participation

Participation will be complete upon completion of the procedures described above. Because participants are healthy volunteers, the only information to be shared would be incidental findings from their medical exam.

5. Management of Data and Samples

a. Storage

After every scanning and behavioral session, all data collected will be de-identified and coded. This includes behavioral measures (e.g., pain reports, reaction time), structural and functional MRI data. Data recorded manually on paper will be entered into computer files. All de-identified data will be stored on password protected NCCIH computers and on secure lab servers hosted by NINDS. All paper questionnaires and forms completed by the subjects will be securely kept in locked drawers in the laboratory/office space of the Principal Investigator. The lab is locked when not occupied. Only study investigators will have access to the data.

b. Data (including genomic data) and sample sharing plan

As no large scale genomic data will be acquired during the course of this protocol, this protocol is not subject to the NIH Genomic Data Sharing (GDS) policy.

Data will be shared with Qualified investigators at NIH or other institutions, including our collaborator on this study, Hakan Olausson (Linkoping University, Sweden)

Data may also be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data from this protocol may be open-access or restricted access.

Data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data and samples may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not

operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

NCCIH specific information on data sharing:
Samples and data may be shared with:

1. Qualified investigators at NIH: For this purpose, investigators will first agree to a data use policy and data will be transferred via methods that limit the chance of others gaining access, such as using a secure file transfer protocol (*sftp*) or restricted access file hosting sites such as *nihcesaev.cit.nih.gov*.
2. Data will be transferred using secure file transfer protocols. Investigators will be allowed to download data after they agree to a data use policy. Some data repositories have their own data use agreement, while others allow the submitter to provide his/her own data use policy. Examples of such repositories include the NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse, www.nitrc.org), the XNAT Central (eXtensible Neuroimaging Archive Toolkit, central.xnat.org), OpenfMRI (OpenfMRI.org), PAIN (Pain and interoceptive imaging network, www.painrepository.org), INCF Dataspace (International Neuroinformatics Coordinating Facility, www.incf.org), 1000 Functional Connectomes and NIDAG (Neuroimaging Data Access Group, www.nidag.org). New data repositories are being created periodically with the intent to facilitate collaboration between research groups with distinct areas of expertise and thus, data collected under this protocol may be contributed to other data repositories not explicitly listed here. Data will only be placed in repositories where access to the data can be restricted to people who accept the data use guidelines and have an account and password that are linked to a valid email address.

- In addition to anatomical and functional MRI images, demographic data such as age and handedness, neuropsychological data such as personality measures and IQ, and behavioral data such as performance on a task, may also be shared. As this protocol concerns studies of brain function in healthy volunteers, no participant has a diagnosed mental health disorder, and there is no risk that such information might be disclosed. Thus, the risk to a participant from sharing their de-identified data is minimal. Depending on the situation, a Global Unique Identifier (GUID) code may be attached to an individual's data prior to sharing or uploading to a repository. When GUID codes are used, only researchers who already have access to someone's personal information can access the code.

6. Additional Considerations

We will be using naloxone at normal clinical doses as the study drug. Naloxone is an opiate antagonist and has been used since the 1960's to reverse the effects of opiate overdoses. The five conditions specified by the FDA for an Exemption for Clinical Investigations involving a Lawfully Marketed Drug (21CFR312.2(B)) are:

"(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for review set forth by an IRB (21CFR56) and the requirements for informed consent (21CFR 50); and

(v) The investigation is conducted in compliance with the requirements of 21CFR 312.7 (Promotion and sale of investigational drugs)."

We believe our use of naloxone meets all five of these conditions. (1) Our investigation is not intended to support a new indication for use of naloxone nor is it intended to support any change in the labeling of the drug. (2) Our investigation is not intended to support a change in the advertising for naloxone. (3) The intravenous route of administration for naloxone in this study is currently an approved route of administration and the dosage we will use is within the normal clinically used range. (4) Our investigation will be conducted in compliance with the requirements of the NIH Neuroscience IRB. (5) The investigation is conducted in compliance with the promotion and sale of investigational drugs.

a. Research with investigational drugs or devices

N/A

b. Gene therapy

N/A

7. Risks and Discomforts

The nature of the study requires the application of hot painful stimuli. However, these stimuli have been used in previous studies, have proven to be easily tolerated, and do not cause permanent tissue damage. A risk of the screening procedures is the results of the drug tests, which will remain documented in the participant's medical record. However, the participants will be informed of this during the telephone pre-screening procedure and asked if they want to continue. If they choose to continue, they will be reminded again during the consenting process.

Risks for 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. Subjects will be screened for these conditions 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.

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 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. 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. There are no known long-term risks of MRI scans.

Risks and discomforts associated with an intravenous line:
The risks of an intravenous catheter include bleeding, infection, or inflammation of the skin and vein, with pain and swelling.

Risks and discomforts associated with naloxone:
Naloxone is an opiate antagonist and is clinically available and commonly used to reverse the adverse effects of opiates, such as remifentanil. Naloxone does not produce respiratory depression, psychotomimetic effects or pupillary constriction. Naloxone has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of opioid dependence, naloxone may produce withdrawal symptoms. While the mechanisms of action of naloxone is not fully understood, most evidence suggests that naloxone antagonizes the opioid effects by competing for the μ, κ, and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor. Following parenteral (outside the intestine) administration, naloxone is rapidly distributed in the body and readily crosses the placenta. Plasma protein binding occurs

but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. Naloxone is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucoronide as the major metabolite. The serum half-life ranges from 30 to 81 minutes (mean 64 ± 12 minutes).

Naloxone is generally thought to be well tolerated and safe. Most of the potential risks associated with naloxone are specific to its precipitating opiate withdrawal and do not apply to its use when patients have no opiates in their system, such as is the case with our study. The most common side effects that have been reported when naloxone is given post-operatively are nausea and vomiting, reversal of pain relief, agitation, and increased or decreased blood pressure. Adverse cardiovascular effects have occurred most frequently in postoperative patients with preexisting cardiovascular disease or in those receiving other drugs that produce similar adverse cardiovascular effects. In experimental studies in subjects not taking opiates (as in our study), the only reported side effects are dry mouth and dizziness. It is important to note that experimental and clinical studies with naloxone have been successfully conducted since the 1960's.

Risks and discomforts associated with heat pain stimuli

Several different sites are stimulated in order to minimize sensitization of the skin. However, reddening of the skin might occur. 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 [37, 40, 46].

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 inflation could dislodge any active blood clots in the participant's leg, so all participants will be checked during medical screening to ensure they do not have any clinical signs of clots present.

Risks and discomfort associated with physiological monitoring

There is no medical risk associated with physiological monitoring. The belts used for respiration monitoring can feel uncomfortable to certain individuals when first attached but this usually subsides.

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 emotional state. Participants will be informed that they can skip any questions they do not wish to answer, and that participation is voluntary.

8. Subject Safety Monitoring

Participants will be monitored by the study investigators during all study visits for study outcomes and adverse events. All subjects will be instructed about, and receive practice with, each test before they begin to perform it and, before a test is formally administered, adequate comprehension of the instructions for each test will be insured by the test examiner.

During an assessment, testers are usually in the room with the subject or in the room just outside the fMRI room. Study staff will monitor individuals during participation and subjects will be encouraged to tell experimenters of any discomfort. If apparatus, etc., cannot be adjusted to relieve discomfort, the experiment will be stopped. Subjects may withdraw at any time.

During MRI scanning, subjects will be given a call button and instructed to use it in case of emergency or if the subject feels any discomfort in the scanner. Throughout the scan session, verbal contact with the subject will be maintained from the control room via an intercom device.

Participants can withdraw from this study at any time and for any reason without loss of benefits or privileges to which they are otherwise entitled or prohibition from enrolling in other clinical protocols. Investigators can remove a participant from the study if an exclusionary condition develops, if the investigator believes that continuation is not in the best medical interest of the subject, or if the subject is unable to comply with study requirements. Sessions

may also be terminated early due to factors that do not directly influence subject safety, such as technical difficulties (e.g. equipment malfunction, computer issues), if schedule conflicts arise (e.g. participant arrives late or needs to leave early; MRI scanner availability is not sufficient to complete the experiment; delays in Clinical Center waiting time, time to process lab orders and lab results). When sessions are terminated early, participants may be asked whether they wish to reschedule. If participants end a session due to discomfort, they will be asked whether they want to continue with other phases of the study, and/or participate in other sub-studies in the protocol.

A. Withdrawal Criteria

Participants can withdraw from this study at any time and for any reason without loss of benefits or privileges to which they are otherwise entitled, or prohibition from enrolling in other clinical protocols. Investigators can remove a participant from the study if an exclusionary condition develops, if the investigator believes that continuation is not in the best medical interest of the subject, or if the subject unable to comply with study requirements.

B. Criteria for Stopping study

In all subjects, procedures will be stopped if requested by participants or if the investigators feel it is in the best interest of the participant.

9. Outcome Measures

a. Primary outcome measures

The primary outcome is the change or difference in pleasantness rating between post-drug and pre-drug of light stroking.

b. Secondary outcome measures

The secondary outcomes include change or differences between post-drug and pre-drug ratings for 1) pleasantness and/or intensity of deep pressure 2) unpleasantness and/or intensity of cutaneous heat pain.)

c. Tertiary outcome measures

1) Determine the role of mood or anxiety changes in mediating the effect of endogenous opioids on these perceptual measures; 2) Determine changes in the brain activation related to these effects.

10. Statistical Analysis

a. Analysis of data/ study outcomes

Testing for normal distribution

All data will be assessed for normality of distribution using the Shapiro Wilk W test. A significant W statistic indicates that the hypothesis of a normal distribution should be rejected, i.e. a significant W indicates skewed data. If the data is skewed the data transformation method will be chosen based on the distribution (Box-Cox method) of the dependent variable. The resulting transformed data will be analyzed with parametric statistics. In the descriptions below we will describe the parametric statistical tests. If data transformation does not work, non-parametric tests will be applied.

Behavioral Data

All behavioral data will be analyzed using SPSS or similar statistical package. A significance level of $p<0.05$ will be adopted for all analyses.

For the primary and secondary outcomes, we will use paired t-test to evaluate the drug effect. To determine whether the effect of drug on touch pleasantness is mediated by mood, we will use Wager & Lindquist's Multilevel Mediation and Moderation (M3) Toolbox. In the analysis, the dependent variables are the sensory ratings, the independent variable is the drug and the mediator variable is mood.

MRI data will be analyzed using standard brain imaging packages such as FSL or AFNI. For the initial analysis, the individual performing the analysis will be blinded. Whole brain analysis will be the first analysis performed followed by analysis looking at individual activations (parameter

estimates) in regions of interest including the insula, cingulate cortex and orbitofrontal cortex. These activations will be used to conduct a mediation analysis of these brain areas in mediating the effect of drug on touch pleasantness ratings. In this analysis, the dependent variables are the perceptual ratings, the independent variable is the level of stimulus and the mediator is the BOLD activation in the brain area of interest (ROI).

b. Power analysis

In order to yield meaningful statistical analyses of the psychophysical data, and specifically for our primary outcome measure, we estimate that the sample size required to complete the study would be 24 healthy participants. G*Power (http://www.gpower.hhu.de) was used to compute the necessary sample size. We used a Cohen's effect size d = 0.61 based on the means and standard deviations of pleasantness rating changes in our previous study of naloxone versus saline [9], statistical power of 80%, and Type I error probability α=0.05. The effect size of 0.61 is clinically important for the pleasantness rating outcome. We expect a 20% dropout rate of participants based on prior NIH studies. Thus, we will enroll up to 30 participants and dropouts will be replaced.

11. Human Subjects Protection

a. Subject selection

Accrual will be equitable among the participants eligible for this study.

b. Justification for exclusion of children

The current study constitutes initial research into the affective mechanisms of light stroking and deep pressure touch and involves procedures such as intravenous drug infusion that are likely to not be well tolerated by children, with no particular benefit to them. In addition, there is evidence that affective touch perception differs by age, both in perception and in brain processing, with children and older adults differing from young and middle-aged adults [47, 48] which would add significant variability to the data. A separate, age-specific study in children is thus warranted and preferable and children will not be included in the current study.

c. Justification for exclusion of other vulnerable subjects

Participants who do not speak English will not be enrolled because our complete set of questionnaires is only validated in English.
Individuals without consent capacity will be excluded because the research question can be answered by enrolling only adults who can consent, and participation does not offer the potential for important clinical benefit. Therefore, the risk outweighs the benefit in this population.

Pregnant women and lactating women are excluded because pregnancy and lactation significantly alter a women's hormonal profile and hormones affect touch processing [49, 50], and because MRI is contraindicated for pregnancy.

Individuals weighing more than 550 lbs. will be excluded because of the weight limit of the MRI scanner.

Because older adults have elevated pain thresholds for brief pain stimuli [51] and there is no evidence that their discriminative functions are unchanged, we are excluding people over 50 years of age.

We will include only right-handed individuals because of increased variability in the lateralization of functions in left-handers, including asymmetries in representations of sensory function [52].

d. Justification for sensitive procedures

N/A

e. Safeguards for vulnerable populations and sensitive procedures

For all fMRI experiments, pregnant women will be excluded from participation due to the unknown effects of the high magnetic field on the developing fetus.

While NCCIH employees are excluded from participation, NIH employees and staff may also be considered vulnerable. Protections for employees and staff participating in this study

include 1) assuring that the participation or refusal to participate will have no effect, either beneficial or adverse, on the subject's employment or position at the NIH, 2) giving employees and staff who are interested in participating the "NIH Information Sheet on Employee Research Participation" prior to obtaining consent, and 3) assuring that there will be no direct solicitation of employees or staff. This study collects sensitive information on drug use and alcohol use and specific medical diagnoses. The PI will train study staff regarding obtaining and handling potentially sensitive and private information about co-workers through staff discussions and written branch/section procedures. Prior to enrollment, potential participants will be informed that this sensitive information will be in their NIH medical record.

12. Anticipated Benefit

The study does not offer direct benefit to participants. However, findings from these studies will contribute to a mechanistic understanding of affective touch, with potential implications for chronic pain.

14. Consent Documents and Process

a. Consent procedures

Informed consent for this study will be obtained in-person at the initial visit or during a separate visit prior to Session 1, after the initial inclusion criteria have been met via the telephone interview and prior to the medical exam or any experimental procedure. The participants will have an opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves. The consent procedures will be conducted in a private room by a qualified study investigator. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. NIH employees will

not be consented by a coworker.

b. Consent documents

The consent form contains all required elements. The consent document is submitted with this protocol.

15. Data and Safety Monitoring

a. Data and safety monitor

The Principal Investigator will be responsible for monitoring data and safety.

b. Data and safety monitoring plan

The Principal Investigator is responsible for maintaining adequate clinical records documenting the medical history, condition and test results for each study participant throughout the study. Source documentation may consist of written or electronic records and supporting data maintained by the PI and/or the institution. The medical records for each participant shall document that informed consent was obtained prior to participation in the study.

Dr. Bushnell will review progress of the study annually. Adverse events data will be reviewed as they arise to ascertain whether or not there are safety concerns with study procedures.

c. Criteria for stopping the study or suspending enrollment or procedures

If there is any serious adverse event (SAE) related to the research, the study will halt until the adverse event and a plan to address the SAE has been resolved by the investigator, clinical director, and the IRB.

16. Quality Assurance

a. Quality assurance monitor

The Principal Investigator is responsible for monitoring the quality assurance of this protocol.

b. Quality assurance plan

On a monthly basis, the PI will review all regulatory and patient information with the study team to ensure data and study integrity are maintained. Data collected on prepared questionnaire forms will be entered into a database against the original source and checked by someone other than the initial person entering data. In addition, this protocol will undergo audits by the QA audit committee as outlined in the NINDS QA Standard Operating Procedure. For studies greater than minimal risk, auditing is conducted in the first year followed by audits q3 year (every third year). The purpose of the QA audit is to assess compliance with applicable regulatory requirements and good clinical practice guidelines, as well as to provide recommendations for improving the management of clinical research data.

17. Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations

Reportable events for this protocol will be tracked and reported in compliance with policy 801.

18. Alternatives to Participation

Subjects do not receive any treatment in this study or forego any treatment in order to participate in this study. The alternative, therefore, is not to participate.

19. Privacy

All research activities will be conducted in as private a setting as possible.

20. Confidentiality

a. For research data and investigator medical records

- 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 in encrypted password-protected NCCIH computers in rooms that are locked

when not occupied. Hard copy records/data will be kept in locked cabinets in rooms that are locked when not occupied. Only study investigators will have access to the data.

- 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.

b. For stored samples

Samples will not be stored. All samples (e.g., urine samples for pregnancy tests and drug screens) will be destroyed.

21. Conflict of Interest

a. Distribution of NIH guidelines

NIH guidelines on conflict of interest have been distributed to all investigators.

b. Conflict of interest

There are no conflicts of interest to report for NIH investigators.

c. Role of a commercial company or sponsor

N/A

22. Technology Transfer

No technology transfer agreement is in place for this protocol.

23. Research and Travel Compensation

Subjects will be compensated for time and research-related inconveniences (see table below) on an hourly basis. If a session cannot be completed due to unforeseen circumstances (e.g., technical issues), payment will be prorated and testing will continue in a rescheduled session. NIH employees and staff who participate during work hours must have permission from their supervisor. NIH employees must either participate outside of work hours or take leave in order to receive compensation. Payment will be made at the completion of each session. No compensation will be made for travel. No escort fees will be provided. The Table below provides the compensation matrix that will be used for research compensation:

Consent (if on separate visit, otherwise part of hourly rate below) Study session (sensory testing with MRI)	$25 $50 per hour, maximum $300 per session
Maximum total compensation	$625

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25. Attachments/ Appendices

Attachment 1: Eligibility Checklist and Pre-Screening Telephone Interview, Pre-Session Screening, MINI

Protocol T-AT-0285 Telephone Pre-screening

Date of Interview: _____ Interviewed By: _____

Hello, this is (INTERVIEWER) calling from NCCIH. Is this _____? Do you have a few minutes to talk about our study on the role of opioids in touch? I'd like to give you a brief description of the study, then you can ask any questions you may have, and then I'll have some questions for you.

In this study, we are interested in the role of opioids on the processing of several types of touch sensations. If you are eligible and choose to participate, you will be scheduled two test sessions. These sessions will occur at least one day apart from each other. During these sessions you will receive naloxone on one day and saline on the other. Naloxone is a drug that temporarily blocks your body's own opioids. The drugs will be given to you intravenously. You will then have an MRI scan and you will receive touch on your leg while under the effects of the drug administered that day. You will be asked to wear shorts or change into scrubs for each session in order to access the lower leg.

During the sensory testing, you will experience light touch with a soft brush, pressure with an inflatable leg wrap, and heat pain sensations using a thermode. The heat you experience will be painful but tolerable. Your skin will not be burned or damaged. You will be asked to provide ratings for the intensity, pain, pleasantness, wanting and liking of each of these sensations as well as ongoing ratings of your mood and anxiety.

The MRI will take up to about 75 minutes. People who are afraid of confined spaces may be anxious in the scanner, and those with back pain may experience discomfort from lying on the scanner surface. The scanner is loud enough to damage hearing, so you will be fitted with hearing protection.

Naloxone, one of the drugs you will receive, is commonly used to reverse the effects of opiates. It has not been shown to produce tolerance or dependence. Most of the associated risks are related to the withdrawal symptoms experienced by those with an opioid dependence. The most common risks reported post-operation are nausea and vomiting, reversal of pain relief, agitation, and changes in blood pressure. However, in studies similar to ours, the only reported side effects are dry mouth and dizziness.

Your urine will be tested for illegal drugs before each study session. If your drug test is positive, you will not be included in the present study. The results of the drug testing will be noted in your NIH medical record. If you do not want this information in your medical record, you should not participate in this study. In addition to this drug screening, participants who are able to become pregnant will have a pregnancy test. If positive, you will not be able to participate because it is unknown if MRI scanning is safe for a developing fetus. We will also document the date of onset of your recent menstrual cycle.

Do you have any questions for me about the study? Are you still interested in participating?

□ YES □ NO

IF YES: Before I schedule you for a screening visit, I will ask questions to verify that you are eligible to participate. Please answer honestly so that we can determine whether it is safe to include you in our study. You don't have to answer questions that you do not feel comfortable answering. All information you provide will remain confidential and, if for some reason you cannot participate, all the information collected will be destroyed.

Subject's Information:

1. Last name: _____ First name: _____

2. Address: _____ City: _____ Zip: _____
3. Best Tel: _____ Email: _____
4. DOB (mm/dd/yyyy): _____/_____/_____
5. Weight _____ (lbs) height: _____
5. Sex: □ M □ F

VERIFYING INCLUSION CRITERIA

CRITERIA	ANSWER	INCLUDE IF
Can you read and speak English easily (fluent in English)?	□ YES □ NO	YES
What is your age?		18≤ or ≤50
Are you able to provide written informed consent?	□ YES □ NO	YES
Administer Edinburgh Handedness Inventory [53]. Right-handed?	Right □ Left □	Right

VERIFYING EXCLUSION CRITERIA

CRITERIA	ANSWER	EXCLUDE IF
Weight 551 lbs or higher?	□ YES □ NO	YES
Do you have a congenital limb deficiency or amputation of a leg?	□ YES □ NO	YES
Have you used recreational drugs in the past month (e.g., marijuana, MDMA ["ecstasy" or "molly"], LSD, cocaine, methamphetamine, heroin, prescription and/or opioids)?	□ YES □ NO	YES
Are you pregnant or breastfeeding?	□ YES □ NO	YES
Are you able to comply with the study procedures and visits? This includes the ability to schedule a second session within 14 days of the first session.	□ YES □ NO	NO
Have you had any dermatological conditions (such as a scar, burn, or tattoo) in the testing region in the last four weeks that might influence the sensitivity of your skin? Any known nerve damage? Any skin area with numbness, prickling/tingling, changed sensitivity to touch or temperature, decreased sense of vibration?	□ YES □ NO	YES
Do you currently suffer from chronic pain or have you suffered from chronic pain in the past year (pain lasting more than 6 months) or do you have ongoing treatment with medications for neuropathic pain (e.g. gabapentin, tricyclic antidepressants, pregabalin, tramadol)	□ YES □ NO	YES
You must be able to lie comfortably flat on your back for up to 75 minutes in the MRI scanner. Do you have claustrophobia or are you uncomfortable in small closed spaces?	□ YES □ NO	YES
Do you have a chronic systemic disease (e.g. diabetes)?	□ YES □ NO	YES

Have you ever been diagnosed with major depression, an anxiety disorder, substance or alcohol dependence or abuse, post-traumatic stress syndrome, bipolar disorder, psychosis, attention-deficit/hyperactivity disorder or attempted suicide? Or do you have ongoing treatment with medications for any of the above (e.g. Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCA), Monoamine oxidase inhibitors (MAOs), Benzodiazepines, Anti-epileptic drugs (AEDs), Hydroxyzine (antihistamine), Antipsychotics, Disulfiram, Varenicline, central stimulants such as Methylphenidate).	□ YES □ NO	YES (if current/lifetime according to MINI)
Do you have a major medical condition such as kidney, liver, pulmonary, autonomic, cardiovascular (e.g. blood clots, hypertension, preexisting cardiac arrhythmia), or neurological disease (e.g., seizure disorder)?	□ YES □ NO Circle which one	YES
Do you currently, or have you ever, had blood clots in your leg?	□ YES □ NO	Yes
Do you have any metal in your body that would make having an MRI scan unsafe? This includes pacemakers, medication pumps, aneurysm clips, shrapnel fragments, permanent eye liner, or small metal fragments in the eye that other metal workers may have.	□ YES □ NO	YES
How many alcoholic beverages do you consume each week? A "standard" drink according to the NIAAA website http://rethinkingdrinking.niaaa.nih.gov/whatcountsdrink/whatsastandarddrink.asp is any drink that contains about 0.6 fluid ounces or 14 grams of "pure" alcohol. This corresponds to: 12 fl oz regular beer (5%) 8-9 fl oz malt beverage (7%) 5 fl oz wine (12%) 3-4 fl oz fortified wine such as sherry, port (17%) 2-3 fl oz cordial liquor or aperitif (24%) 1.5 fl oz brandy (40%) 1.5 fl oz shot or 80-proof spirit (hard liquor) (40%)	Regular beer: Strong beer: Wine: Fortified wine: Cordial Liquor: Brandy-like: Shots/hard liquor:	Women: > 7 Men: > 14
Are you an NIH employees who is subordinate, a relative, or co-worker of any of the investigators, or are you an NCCIH DIR employee?	□ YES □ NO	YES
Do you have allergies to naloxone or similar drugs?	□ YES □ NO	YES
Do you use any medications that may affect opioid pathways (e.g. loperamide or dextromethorphan), could potentially interact with naloxone (naltrexone, methylnaltrexone, droperidol, fenfluramine and clonidine)	□ YES □ NO	YES
Do you use any herbal preparations (such as yohimbine)?	□ YES □ NO	YES

EVALUATION OF MEDICATION USE

Have you taken any medication in the last 30 days other than over-the-counter NSAIDs or acetaminophen, including OTC, RX, topical pain-relieving creams?

Medication / Treatment	Indication	Dosage/ Interval	Start Date	End Date	Comments

If unclear: Thank you. I'll discuss this information with my team to make sure you're a good match for our study and I'll contact you soon.

Date of follow up call: (mm/dd/yyyy): _____/_____/_____; Time: _____ AM/PM

If not eligible: Unfortunately, it doesn't look like this study is a good match for you. I am going to shred the information you gave me. If you'd like to find other studies that might be a better match, you can get in touch with the clinical recruiting office or go online to Clinicaltrials.gov *(If exclude, log and shred)*

If eligible: It looks like you would be a good match for our study. I'd like to go ahead and schedule you for your first visit.

If they're new add: "You will need to go through a separate admissions process with the NIH before your begin your visit with us and that can take anywhere between 15 minutes and an hour depending on how many other people are there that day."

☐	Discussed communication for scheduling.	Prefers (circle one): Phone Email
☐	Would you like me to send you: the consent form, map/directions, appointment confirmation?	
☐	Discussed compensation	• Study session (Sensory testing with MRI): $150 each, $300 total for study
☐	Explained transportation	Transportation will not be reimbursed but free parking is available (validation).
☐	Updated enrollment log and assigned subject code	

SCHEDULE SESSION 1 _____; Time: _____

REMINDER: If you consume alcohol or use pain medications or pain-relieving creams on the testing area in the 24 hours prior to your session, we will need to reschedule your session. We will email or call you the day before your appointment. Please contact me if you have any questions between now and your appointment

In-Person Screening Form

Subject ID: _____ Date _____

Session 1

If participant answers YES to one or more questions below, they will be rescheduled up to two times rather than excluded (participants with positive pregnancy tests will be excluded, however). If the participant is found non-compliant, i.e., answered YES to one or more questions below, during the second rescheduled appointment, he or she will be excluded from the study. All eligibility criteria will also be reviewed and confirmed by a LHP.

CRITERIA	ANSWER	RESCHEDULE EXCLUDE IF
Drug test (tox screen)	□ POS □ NEG	POS
Pregnancy test (those able to become pregnant)	□ POS □ NEG	YES
In the last 24 hours, have you consumed alcohol?	□ YES □ NO	YES
Is the participant showing behavioral signs of intoxication? • Speech: overly talkative, argumentative, opinionated or interrupting; stumbling over words; loud, inappropriate language or jokes • Coordination: slowed or delayed reactions, stagger, swagger, or sway • Appearance: vacant or blank expression, smell of alcohol on breath, untidy appearance • Behavior: overly friendly or withdrawn, inappropriate or risky actions, attention difficulties	□ YES □ NO	YES
Is the participant showing signs of alcohol withdrawal syndrome (e.g. symptoms of hand tremors, irregular heart rate, fever, nausea, sweating, dehydration, headache, or confusion)?	□ YES □ NO	YES
In the last 24 hours, have you used a topical pain-relieving cream (e.g. methylsalicylate, capsaicin) on your arms?	□ YES □ NO	YES
In the last 3 days, have you used any non-steroidal anti-inflammatory drug (NSAID) and/or over-the-counter drug (e.g., aspirin, ibuprofen, acetaminophen, naproxen)?	□ YES □ NO	YES

SCHEDULE SESSION 2 _____; Time: _____

REMINDER: If you consume alcohol or use pain medications or pain-relieving creams on the testing area in the 24 hours prior to your session, we will need to reschedule your session. We will email or call you the day before your appointment. Please contact me if you have any questions between now and your appointment

Session 2

All eligibility criteria will also be reviewed with an LHP to confirm there are no changes.

CRITERIA	ANSWER	RESCHEDULE IF
Drug test (tox screen)	□ POS □ NEG	POS
Pregnancy test (those able to become pregnant)	□ POS □ NEG	**EXCLUDE**
In the last 24 hours, have you consumed alcohol?	□ YES □ NO	YES
Is the participant showing behavioral signs of intoxication? • Speech: overly talkative, argumentative, opinionated or interrupting; stumbling over words; loud, inappropriate language or jokes • Coordination: slowed or delayed reactions, stagger, swagger, or sway • Appearance: vacant or blank expression, smell of alcohol on breath, untidy appearance • Behavior: overly friendly or withdrawn, inappropriate or risky actions, attention difficulties	□ YES □ NO	YES
Is the participant showing signs of alcohol withdrawal syndrome (e.g. symptoms of hand tremors, irregular heart rate, fever, nausea, sweating, dehydration, headache, or confusion)?	□ YES □ NO	YES
In the last 24 hours, have you used a topical pain-relieving cream (e.g. methylsalicylate, capsaicin) on your arms?	□ YES □ NO	YES
In the last 3 days, have you used any non-steroidal anti-inflammatory drug (NSAID) and/or over-the-counter drug (e.g., aspirin, ibuprofen, acetaminophen, naproxen, sumatriptan)?	□ YES □ NO	YES

If any of the questions regarding behavioural signs of intoxication or signs of alcohol withdrawal are answered **YES** the subject should be immediately excluded and not rescheduled.

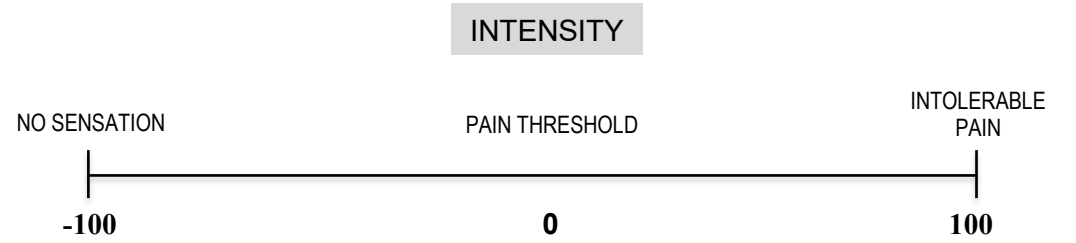
If one or more other question answers are **YES**:

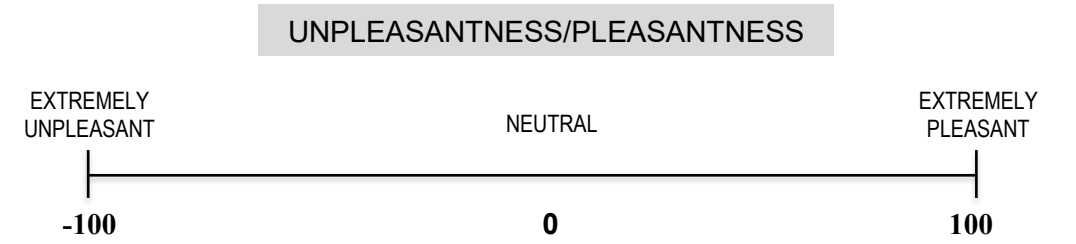
Is this the <u>first</u> or <u>second</u> time the participant will be rescheduled? (circle one)

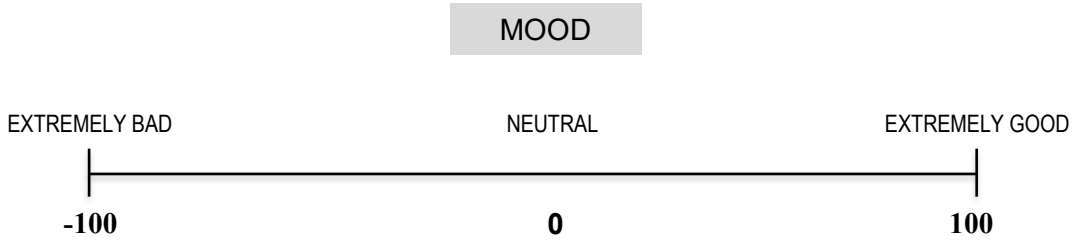
Rescheduled Appointment:

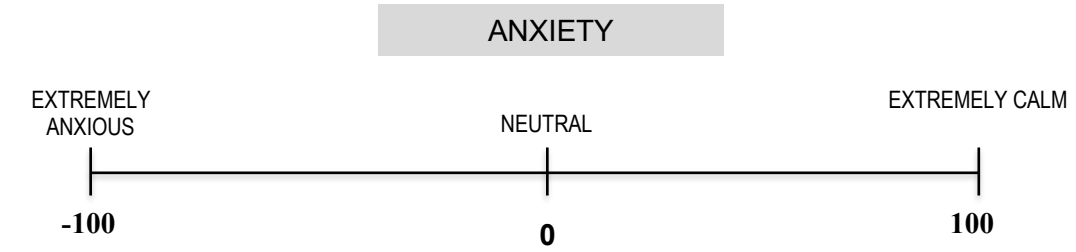
Date (mm/dd/yyyy): _____/_____/_____ Time: _____ AM/PM

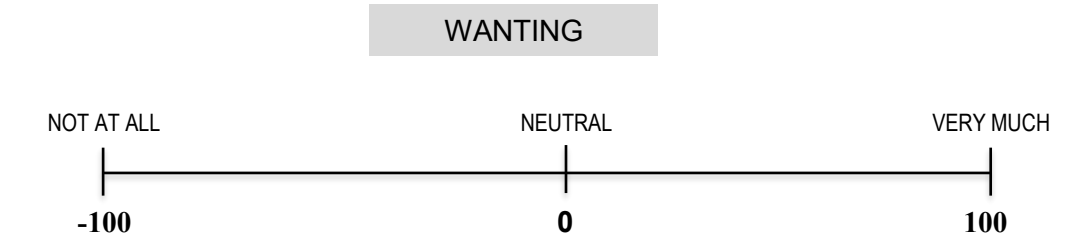
Attachment 2: Rating Scales, and Questionnaires: TCI, HADS, BI/BAS, NEO-FFI-3, STQ

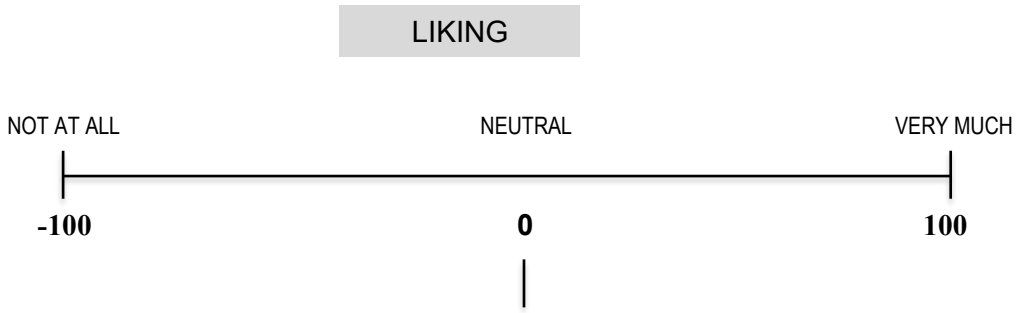












Temperament and Character Inventory
TCI

How to fill out this questionnaire

To answer you only need to circle either "T" (True) or "F" (False) after each question.

Read each statement carefully, but don't spend too much time deciding on the answer.

Please answer every statement, even if you are not completely sure of the answer.

Remember that there are no right or wrong answers – just describe you own personal opinions and feelings.

			True	False
1.	(1)	I often try new things just for fun or thrills, even if most people think it is a waste of time.	T	F
2.	(2)	I usually am confident that everything will go well, even in situations that worry most people.	T	F
3.	(3)	I am often moved deeply by a fine speech or poetry.	T	F
4.	(11)	I could probably accomplish more than I do, but I don't see the point in pushing myself harder than is necessary to get by.	T	F

5.	(12)	I often feel tense and worried in unfamiliar situations, even when others feel there is little to worry about.	T	F
6.	(13)	I often do things based on how I feel at the moment without thinking how they were done in the past.	T	F
7.	(14)	I usually do things my own way – rather than giving in to the wishes of other people.	T	F
8.	(19)	I am much more reserved and controlled than most people.	T	F
9.	(20)	I often have to stop what I am doing because I start worrying about what might go wrong.	T	F
10.	(21)	I like to discuss my experiences and feelings openly with friends instead of keeping them to myself.	T	F
11.	(22)	I have less energy and get tired more quickly than most people.	T	F
12.	(26)	Most of the time I would prefer to do something a little risky (like riding in an automobile over steep hills and sharp turns) – rather than having to stay quiet and inactive for a few hours.	T	F
13.	(27)	I often avoid meeting strangers because I lack confidence with people I do not know.	T	F
14.	(28)	I like to please other people as much as I can.	T	F
15.	(29)	I like old "tried and true" ways of doing things much better than trying "new and improved" ways.	T	F
16.	(34)	I like to be very organized and set up rules for people whenever I can.	T	F
17.	(35)	It is difficult for me to keep the same interests for a long time because my attention often shifts to something else.	T	F
18.	(37)	I am usually so determined that I continued to work long after other people have given up.	T	F

19.	(41)	I often spend money until I run out of cash or get into debt from using too much credit.	T	F
20.	(42)	I think I will have very good luck in the future.	T	F
21.	(43)	I recover more slowly than other people from minor illnesses or stress.	T	F
22.	(44)	It wouldn't bother me to be alone all the time.	T	F
23.	(46)	I don't care very much whether other people like me or the way I do things.	T	F
24.	(52)	In conversations I am much better as a listener than as a talker.	T	F
25.	(53)	I lose my temper more quickly than most people.	T	F
26.	(54)	When I have to meet a group of strangers, I am more shy than most people.	T	F
27.	(55)	I am more sentimental than most people.	T	F
28.	(61)	I like to think about things for a long time before I make a decision.	T	F
29.	(62)	I am more hard-working than most people.	T	F
30.	(63)	I often need naps or extra rest periods because I get tired so easily.	T	F
31.	(65)	Regardless of any temporary problem that I have to overcome, I always think it will turn out well.	T	F
32.	(66)	It is hard for me to enjoy spending money on myself, even when I have saved plenty of money.	T	F
33.	(67)	I usually stay calm and secure in situations that most people would find physically dangerous.	T	F
34.	(68)	I like to keep my problems to myself	T	F
35.	(70)	I like to stay at home better than to travel or explore new places.	T	F

36.	(71)	I do not think it is smart to help weak people who cannot help themselves.	T	F
37.	(79)	I like it when people can do whatever they want without strict rules and regulations.	T	F
38.	(80)	I would probably stay relaxed and outgoing when meeting a group of strangers, even if I were told they are unfriendly.	T	F
39.	(81)	Usually I am more worried than most people that something might go wrong in the future.	T	F
40.	(82)	I usually think about all the facts in detail before I make a decision.	T	F
41.	(83)	I feel it is more important to be sympathetic and understanding of other people than to be practical and tough-minded	T	F
42.	(91)	I am usually able to get other people to believe me, even when I know that what I am saying is exaggerated or untrue.	T	F
43.	(92)	I need much extra rest, support, or reassurance to recover from minor illnesses or stress.	T	F
44.	(99)	I have a reputation as someone who is very practical and does not act on emotion.	T	F
45.	(100)	It is easy for me to organize my thoughts while talking to someone.	T	F
46.	(102)	I am strongly moved by sentimental appeals (like when asked to help crippled children)	T	F
47.	(103)	I usually push myself harder than most people do because I want to do as well as I possibly can.	T	F
48.	(108)	I hate to make decisions based only on my first impressions.	T	F
49.	(109)	I prefer spending money rather than saving it.	T	F
50.	(110)	I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone.	T	F

51.	(112)	If I am embarrassed or humiliated, I get over it very quickly.	T	F
52.	(113)	It is extremely difficult for me to adjust to change in my usual way of doing things because I get so tense, tired, or worried.	T	F
53.	(114)	I usually demand very good practical reasons before I am willing to change my old ways of doing things.	T	F
54.	(117)	I would like to have warm and close friends around with me most of the time.	T	F
55.	(119)	I nearly always stay relaxed and carefree, even when nearly everyone else is fearful.	T	F
56.	(120)	I find sad songs and movies pretty boring.	T	F
57.	(128)	I am satisfied with my accomplishments, and have little desire to do better.	T	F
58.	(129)	I often feel tense and worried in unfamiliar situations, even when others feel there is no danger at all.	T	F
59.	(130)	I often follow my instincts, hunches, or intuition without thinking through all the details.	T	F
60.	(131)	Other people often think that I am too independent because I won't do what they want.	T	F
61.	(139)	I am better at saving money than most people.	T	F
62.	(141)	Even when most people feel it is not important, I often insist on things being done in a strict and orderly way.	T	F
63.	(142)	I feel very confident and sure of myself in almost all social situations.	T	F
64.	(143)	My friends find it hard to know my feelings because I seldom tell them about my private thoughts.	T	F
65.	(144)	I hate to change the way I do things, even if many people tell me there is a new and better way to do it.	T	F
66.	(147)	I am more energetic and tire less quickly than most people.	T	F

67.	(148)	I like to pay close attention to details in everything I do.	T	F
68.	(149)	I often stop what I am doing because I get worried, even when my friends tell me everything will go well.	T	F
69.	(154)	Most of the time I would prefer to do something risky (like hand-gliding or parachute jumping) – rather than having to stay quiet and inactive for a few hours.	T	F
70.	(155)	Because I so often spend too much money on impulse, it is hard for me to save money – even for special plans like a vacation.	T	F
71.	(156)	I don't go out of my way to please other people.	T	F
72.	(157)	I am not shy with strangers at all.	T	F
73.	(158)	I often give in to the wishes of friends.	T	F
74.	(164)	I never worry about terrible things that might happen in the future.	T	F
75.	(165)	I almost never get so excited that I lose control of myself.	T	F
76.	(166)	I often give up a job if it takes much longer than I thought it would.	T	F
77.	(167)	I prefer to start conversations, rather than waiting for other to talk to me.	T	F
78.	(174)	It is fun for me to buy things for myself.	T	F
79.	(180)	I usually like to stay cool and detached from other people.	T	F
80.	(181)	I am more likely to cry at a sad movie than most people.	T	F
81.	(182)	I recover more quickly than most people from minor illnesses or stress.	T	F
82.	(183)	I often break rules and regulations when I think I can get away with it.	T	F

83.	(187)	I like to make quick decisions so I can get on with what has to be done.	T	F
84.	(188)	I usually have good luck in whatever I try to do.	T	F
85.	(189)	I am usually confident that I can do things that most people would consider dangerous (such as driving an automobile fast on a wet or icy road).	T	F
86.	(191)	I like to explore new ways to do things.	T	F
87.	(192)	I enjoy saving money more than spending it on entertainment or thrills.	T	F
88.	(193)	Individual rights are more important than the needs of any group.	T	F
89.	(201)	Even when I am with friends, I prefer not to "open up" very much.	T	F
90.	(202)	I usually can stay "on the go" all day without having to push myself.	T	F
91.	(203)	I nearly always think of all the facts in detail before I make a decision, even when other people demand a quick decision.	T	F
92.	(204)	I am not very good at talking my way out of trouble when I am caught doing something wrong.	T	F
93.	(205)	I am more of a perfectionist than most people.	T	F
94.	(209)	I think I would stay confident and relaxed when meeting strangers, even if I were told they are angry at me.	T	F
95.	(210)	People find it easy to come to me for help, sympathy, and warm understanding.	T	F
96.	(211)	I am slower than most people to get excited about new ideas and activities.	T	F
97.	(212)	I have trouble telling a lie, even when it is meant to spare someone else's feeling.	T	F

98.	(217)	I usually feel tense and worried when I have to do something new and familiar.	T	F
99.	(218)	I often push myself to the point of exhaustion or try to do more than I really can.	T	F
100.	(219)	Some people think I am too stingy or tight with my money.	T	F
101.	(224)	I regularly take time to consider whether what I am doing is right or wrong.	T	F
102.	(225)	Things often go wrong for me unless I am very careful.	T	F
103.	(226)	If I am feeling upset, I usually feel better around friends than when left alone.	T	F
104.	(231)	I usually stay away from social situations where I would have to meet strangers, even if I am assured that they will be friendly.	T	F
105.	(236)	I usually feel much more confident and energetic than most people, even after minor illnesses or stress.	T	F
106.	(237)	I like to read everything when I am asked to sign any papers.	T	F
107.	(238)	When nothing new is happening, I usually start looking for something that is thrilling or exciting.	T	F

Hospital Anxiety and Depression Scale (HADS)

Name _____
Date _____

We would like to know how the following statements currently describe your feelings. **Please choose one response from the four given for each statement. Give us your immediate response and don't think too long about your answers. Please go through all 14 statements and do not miss a statement.**

Thank you

1	**I feel tense or 'wound up':**	
	Most of the time	
	A lot of the time	
	From time to time, occasionally	
	Not at all	

2	**I still enjoy the things I used to enjoy:**	
	Definitely as much	
	Not quite so much	
	Only a little	
	Hardly at all	

3	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	
	Yes, but not too badly	
	A little, but it doesn't worry me	
	Not at all	

4	**I can laugh and see the funny side of things:**	
	As much as I always could	
	Not quite so much now	
	Definitely not so much now	
	Not at all	

5	**Worrying thoughts go through my mind:**	
	A great deal of the time	
	A lot of the time	
	From time to time, but not too often	
	Only occasionally	

6	**I feel cheerful:**	
	Not at all	
	Not often	
	Sometimes	
	Most of the time	

7	**I can sit at ease and feel relaxed:**	
	Definitely	
	Usually	
	Not Often	
	Not at all	

8	**I feel as if I am slowed down:**	
	Nearly all the time	
	Very often	
	Sometimes	
	Not at all	

9	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	
	Occasionally	
	Quite Often	
	Very Often	

10	**I have lost interest in my appearance:**	
	Definitely	
	I don't take as much care as I should	
	I may not take quite as much care	
	I take just as much care as ever	

11	**I feel restless as I have to be on the move:**	
	Very much indeed	
	Quite a lot	
	Not very much	
	Not at all	

12	**I look forward with enjoyment to things:**	
	As much as I ever did	
	Rather less than I used to	
	Definitely less than I used to	
	Hardly at all	

13	**I get sudden feelings of panic:**	
	Very often indeed	
	Quite often	
	Not very often	
	Not at all	

14	**I can enjoy a good book or radio or TV program:**	
	Often	
	Sometimes	
	Not often	
	Very seldom	

BEHAVIORAL AND APPETITIVE SYSTEM SCALE
(BIS/BAS)

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life. ____
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness. ____
3. I go out of my way to get things I want. ____
4. When I'm doing well at something I love to keep at it. ____
5. I'm always willing to try something new if I think it will be fun. ____
6. How I dress is important to me. ____
7. When I get something I want, I feel excited and energized. ____
8. Criticism or scolding hurts me quite a bit. ____
9. When I want something I usually go all-out to get it. ____
10. I will often do things for no other reason than that they might be fun. ____
11. It's hard for me to find the time to do things such as get a haircut. ____
12. If I see a chance to get something I want I move on it right away. ____
13. I feel pretty worried or upset when I think or know somebody is angry at me. ____
14. When I see an opportunity for something I like I get excited right away. ____
15. I often act on the spur of the moment. ____
16. If I think something unpleasant is going to happen I usually get pretty "worked up". ____
17. I often wonder why people act the way they do. ____
18. When good things happen to me, it affects me strongly. ____
19. I feel worried when I think I have done poorly at something important. ____
20. I crave excitement and new sensations. ____
21. When I go after something I use a "no holds barred" approach. ____
22. I have very few fears compared to my friends. ____
23. It would excite me to win a contest. ____
24. I worry about making mistakes. ____

NEO™-FFI-3

NEO Five-Factor Inventory-3

Paul T. Costa, Jr., PhD and Robert R. McCrae, PhD

Item Booklet | **Form S–Adult**

SELF-REPORT

Instructions

Write only where indicated in this Item Booklet. Carefully read all of the instructions before beginning. This questionnaire contains 60 statements. Read each statement carefully. For each statement, fill in the circle with the response that best represents your opinion. Make sure that your answer is in the correct box.

Fill in (SD) if you *strongly disagree* or the statement is definitely false.

Fill in (D) if you *disagree* or the statement is mostly false.

Fill in (N) if you are *neutral* on the statement, if you cannot decide, or if the statement is about equally true and false.

Fill in (A) if you *agree* or the statement is mostly true.

Fill in (SA) if you *strongly agree* or the statement is definitely true.

Note that the responses are numbered in ***rows***.

Example

First five responses from an individual who strongly disagrees with items 1, 2, and 3, and agrees with items 4 and 5.

Fill in only one response for each statement. Respond to all of the statements, making sure that you fill in the correct response. **DO NOT ERASE**! If you need to change an answer, make an "**X**" through the incorrect response and then fill in the correct response.

Before responding to the statements, turn to the inside of this Item Booklet and enter your name, age, sex, ID number (if any), and today's date.

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ID# _____

Name _____ Age _____ Sex _____ Today's date _____

1. I am not a worrier.
2. I like to have a lot of people around me.
3. I enjoy concentrating on a fantasy or daydream and exploring all its possibilities, letting it grow and develop.
4. I try to be courteous to everyone I meet.
5. I keep my belongings neat and clean.
6. At times I have felt bitter and resentful.
7. I laugh easily.
8. I think it's interesting to learn and develop new hobbies.
9. At times I bully or flatter people into doing what I want them to.
10. I'm pretty good about pacing myself so as to get things done on time.
11. When I'm under a great deal of stress, sometimes I feel like I'm going to pieces.
12. I prefer jobs that let me work alone without being bothered by other people.
13. I am intrigued by the patterns I find in art and nature.
14. Some people think I'm selfish and egotistical.
15. I often come into situations without being fully prepared.
16. I rarely feel lonely or blue.
17. I really enjoy talking to people.
18. I believe letting students hear controversial speakers can only confuse and mislead them.
19. If someone starts a fight, I'm ready to fight back.
20. I try to perform all the tasks assigned to me conscientiously.
21. I often feel tense and jittery.
22. I like to be where the action is.
23. Poetry has little or no effect on me.
24. I'm better than most people, and I know it.
25. I have a clear set of goals and work toward them in an orderly fashion.
26. Sometimes I feel completely worthless.
27. I shy away from crowds of people.
28. I would have difficulty just letting my mind wander without control or guidance.
29. When I've been insulted, I just try to forgive and forget.
30. I waste a lot of time before settling down to work.
31. I rarely feel fearful or anxious.
32. I often feel as if I'm bursting with energy.
33. I seldom notice the moods or feelings that different environments produce.
34. I tend to assume the best about people.
35. I work hard to accomplish my goals.
36. I often get angry at the way people treat me.
37. I am a cheerful, high-spirited person.
38. I experience a wide range of emotions or feelings.
39. Some people think of me as cold and calculating.
40. When I make a commitment, I can always be counted on to follow through.

41. Too often, when things go wrong, I get discouraged and feel like giving up.
42. I don't get much pleasure from chatting with people.
43. Sometimes when I am reading poetry or looking at a work of art, I feel a chill or wave of excitement.
44. I have no sympathy for beggars.
45. Sometimes I'm not as dependable or reliable as I should be.

46. I am seldom sad or depressed.
47. My life is fast-paced.
48. I have little interest in speculating on the nature of the universe or the human condition.
49. I generally try to be thoughtful and considerate.
50. I am a productive person who always gets the job done.

51. I often feel helpless and want someone else to solve my problems.
52. I am a very active person.
53. I have a lot of intellectual curiosity.
54. If I don't like people, I let them know it.
55. I never seem to be able to get organized.

56. At times I have been so ashamed I just wanted to hide.
57. I would rather go my own way than be a leader of others.
58. I often enjoy playing with theories or abstract ideas.
59. If necessary, I am willing to manipulate people to get what I want.
60. I strive for excellence in everything I do.

Enter your responses here—remember to enter responses *ACROSS* the rows.

SD = *Strongly Disagree*; D = *Disagree*; N = *Neutral*; A = *Agree*; SA = *Strongly Agree*

ENTER ACROSS ⇨

1 (SD) D N A SA	2 (SD) D N A SA	3 (SD) D N A SA	4 (SD) D N A SA	5 (SD) D N A SA
6 (SD) D N A SA	7 (SD) D N A SA	8 (SD) D N A SA	9 (SD) D N A SA	10 (SD) D N A SA
11 (SD) D N A SA	12 (SD) D N A SA	13 (SD) D N A SA	14 (SD) D N A SA	15 (SD) D N A SA
16 (SD) D N A SA	17 (SD) D N A SA	18 (SD) D N A SA	19 (SD) D N A SA	20 (SD) D N A SA
21 (SD) D N A SA	22 (SD) D N A SA	23 (SD) D N A SA	24 (SD) D N A SA	25 (SD) D N A SA
26 (SD) D N A SA	27 (SD) D N A SA	28 (SD) D N A SA	29 (SD) D N A SA	30 (SD) D N A SA
31 (SD) D N A SA	32 (SD) D N A SA	33 (SD) D N A SA	34 (SD) D N A SA	35 (SD) D N A SA
36 (SD) D N A SA	37 (SD) D N A SA	38 (SD) D N A SA	39 (SD) D N A SA	40 (SD) D N A SA
41 (SD) D N A SA	42 (SD) D N A SA	43 (SD) D N A SA	44 (SD) D N A SA	45 (SD) D N A SA
46 (SD) D N A SA	47 (SD) D N A SA	48 (SD) D N A SA	49 (SD) D N A SA	50 (SD) D N A SA
51 (SD) D N A SA	52 (SD) D N A SA	53 (SD) D N A SA	54 (SD) D N A SA	55 (SD) D N A SA
56 (SD) D N A SA	57 (SD) D N A SA	58 (SD) D N A SA	59 (SD) D N A SA	60 (SD) D N A SA

Now answer the three questions labeled A, B, and C below.

A. Have you responded to all of the statements? ____ Yes ____ No

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SOCIAL TOUCH QUESTIONNAIRE

Indicate how characteristic or true each of the following statements is of you:

0-4 scale (0 = not at all, 1 = slightly, 2 = moderately, 3 = very, 4 = extremely)

	0	1	2	4	5
I generally like when people express their affection towards me in a physical way					
I feel uncomfortable when someone I don't know very well hugs me					
I get nervous when an acquaintance keeps holding my hand after a handshake					
I generally seek physical contact with others					
I feel embarrassed if I have to touch someone in order to get their attention					
I consider myself to be a 'touchy-feely' person					
It annoys me when someone touches me unexpectedly					
I'd feel uncomfortable if a professor touched me on the shoulder in public					
I'd be happy to give a neck/shoulder massage to a friend if they are feeling stressed					
I feel uncomfortable if I make physical contact with a stranger on the bus or subway					
I like being caressed in intimate situations					

As a child, I was often cuddled by family members (e.g. parents, siblings)					
I would rather avoid shaking hands with strangers					
I greet my close friends with a kiss, cheek-to-cheek					
I feel comfortable touching people I do not know very well					
I feel disgusted when I see public displays of intimate affection					
It would make me feel anxious if someone I had just met touched me on the wrist					
If I had the means, I would get weekly professional massages					
I hate being tickled					
I like petting animals					

APPENDIX II

Medical Research Council Speech & Communication Unit

EDINBURGH HANDEDNESS INVENTORY

Surname..... Given Names.....

Date of Birth ..... Sex.....

Please indicate your preferences in the use of hands in the following activities *by putting + in the appropriate column.* Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put ++.* If in any case you are really indifferent *put + in both columns.*

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking Match (match)		
10	Opening box (lid)		
i	Which foot do you prefer to kick with?		
ii	Which eye do you use when using only one?		

L.Q.		Leave these spaces blank	DECILE	

MARCH 1970

Attachment 3: Precis for clinicaltrials.gov

Précis:

Objective: Our sense of touch includes the intensity, pleasantness and unpleasantness of touch. There is some evidence that opioids affect the perception of touch and that blocking endogenous opioid release alters perception of touch and pain. The current study will examine the role of endogenous opioids in the perception of light skin stroking, deep pressure touch, and painful heat. Further, it will examine the neural basis of observed perceptual changes, using fMRI.

Study Population: 30 healthy participants will be enrolled in the study.

Design: Participants will receive intravenous saline or intravenous naloxone on separate days to investigate the effect of mu-opioid antagonism on the intensity and pleasantness of superficial and deep affective touch and the intensity and unpleasantness of cutaneous heat pain. Using a double-blind cross-over design, functional Magnetic Resonance Imaging (fMRI) will be conducted during sensory testing before and after the infusion of each drug to examine the neural mediation of opioid effects on touch perception. Ratings of mood, anxiety, pain intensity, pleasantness/unpleasantness, wanting and liking will also be collected throughout the study session.

Outcome measures: We will compare subjective ratings (mood, calmness, anxiety, pleasantness, unpleasantness, wanting, liking, pain intensity and unpleasantness) during naloxone and saline to: 1) Determine whether naloxone alters the pleasantness and/or intensity of affective touch (light brush and deep compression); 2) Determine whether naloxone alters the unpleasantness and/or intensity of cutaneous heat pain; 3) Determine the role of mood or anxiety changes in mediating the effect of endogenous opioids on these perceptual measures; 3) Determine changes in the brain activation related to these effects.

26. Consent Forms

Please see separate Consent Form document.