Protocol Title: Sensory Afferents for Deep Pressure Sensation
Abbreviated Title: Afferents for Deep Pressure
Protocol Number: **19-AT-0089**
Version Date / Number: November 19, 2020, Version 2.3

Principal Investigator

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Medical Advisory Investigator

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:

- Biomedical- Vulnerable Subjects- Workers/Employees
- Unanticipated Problems and Reporting Requirements in Social and Behavioral Research
- CITI GCP modules

Total requested accrual
24 Healthy Volunteers

Project Uses Ionizing Radiation: ✠ 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

Covered Protocol Requiring DEC Clearance (per SOP 21) ✠ No ☐ Yes

Approved for Short Form Consent Process for Non-English Speakers ✠ No ☐ Yes

Flesch-Kincaid reading level of consent form: ____8.8_____

Précis:

Objective: The sensory basis of non-painful deep pressure sensation is not known. We recently found that innocuous pressure sensation is eliminated in rare sensory neuronopathy patients with a specific loss of A-beta fibers, strongly suggesting that A-beta fibers underlie the ability to sense deep pressure. In addition, we and others have shown that deep pressure touch (observed in hugs and massage) frequently conveys a sense of pleasantness. The current study aims to examine the role of A-beta fibers in the perception of deep pressure touch including both its intensity and the pleasant affect it often elicits. This study constitutes the second study of the K99 phase of a K99/R00 grant application awarded to Dr. Laura Case by NCCIH.

Study Population: Up to 24 healthy participants will be enrolled in the study with a goal of 12 completers. Participants will be invited based on previous screening and participation in our studies.

Design: Participants will undergo an ischemic-compression block. Sensory stimuli will be administered at frequent intervals to capture the loss of sensation related to A fibers as the block progresses. Before and after A-beta-associated sensations have been lost, the perception of deep pressure will be tested. Participants will rate the intensity and pleasantness of the pressure. Ratings of pain and discomfort will be collected throughout the study session.

Outcome measures: Primary outcome; Rating of intensity of deep pressure on the blocked arm before versus after loss of A-beta sensation, compared to ratings on the unblocked arm.
Secondary outcomes: 1) Rating of pleasantness of deep pressure on the blocked arm after loss of A-beta sensation, compared to ratings on the unblocked arm; 2) Ratings of intensity and pleasantness of gentle brushing on the blocked arm after loss of A-beta sensation, compared to ratings on the unblocked arm.

Precis posted online at clinicaltrials.gov: see Attachment 2

Table of Contents

Précis: 2
List of Abbreviations 4
1. Introduction and Background 4
2. Study Objectives 7
3. Subjects 7
Exclusion criteria for individual study session 8
4. Study Design and Methods 9
5. Management of Data and Samples 16
6. Additional Considerations 18
7. Risks and Discomforts 18
8. Subject Safety Monitoring 20
9. Outcome Measures 21
10. Statistical Analysis 22
11. Human Subjects Protection 23
12. Anticipated Benefit 25
14. Consent Documents and Process 25
15. Data and Safety Monitoring 26
16. Quality Assurance (QA) 26
17. Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations 27
18. Alternatives to Participation 27
19. Privacy 27
20. Confidentiality 27
21. Conflict of Interest 28
22. Technology Transfer 28
23. Research and Travel Compensation 28
24. References 30
25. Attachments/Appendices 32
26. Consent Forms 38

List of Abbreviations

BP = Blood Pressure
C-LTMR = C Low Threshold Mechanoreceptors
CRIS = Clinical Research Information System
DEC = Deputy Ethics Counselor
DIR = Division of Intramural Research
DoH = Declaration of Helsinki
FWA= Federal Wide Assurance
GUID = Global Unique Identifier
HRPP = Human Research Protection Program
Hz = Hertz
INCF = International Neuroinformatics Coordinating Facility
IRB = Institutional Review Board
iRIS = Integrated Research Information System
IRTA = Intramural Research Training Award
LHP = Licensed Healthcare Practitioner
mmHg = Millimeter of Mercury
NCCIH = National Center for Complementary and Integrative Health
NIDAG = Neuroimaging Data Access Group
NIH = National Institutes of Health
NINR = National Institute of Nursing Research
NITRC = Neuroimaging Informatics Tools and Resources Clearinghouse
NRS = Numeric Ratings Scale
NSAIDs = Nonsteroidal Anti-Inflammatory Drugs
OHSRP = Office for Human Subjects Research Protections
PAIN = Pain and Interoception Imaging Network
PI = Principal Investigator
QA = Quality Assurance
SAE = Serious Adverse Event
SOP = Standard Operating Procedure
SPSS = Statistical Package for the Social Sciences
UP = Unanticipated Problem
VAS = Visual Analogue Scale
XNAT = eXtensible Neuroimaging Archive Toolkit

1. Introduction and Background

Deep pressure is a critical component of many touch therapies including massage therapy. However, the sensory basis of non-painful deep pressure perception is not known. A better understanding of the mechanism of deep pressure sensation in humans is important for understanding the mechanisms of manual therapies, as well as for

understanding pain-related changes in deep muscle sensation in individuals with chronic pain. Here, we investigate the role of myelinated (A) and unmyelinated (C) sensory afferents in the perception of deep pressure sensation. We hypothesize that A-beta fibers underlie both the intensity and pleasantness of innocuous deep pressure sensation.

Myelinated and unmyelinated sensory afferents innervate not only the epidermis but also muscle and connective tissues, and even bones [1, 2]. Numerous studies have shown the existence of unmyelinated muscle afferents with nociceptive properties, but little is known about sensations associated with the other afferent types innervating deeper tissues [3]. However, there is evidence that sensations of deep pressure also involve activation of sensory afferents below the level of the epidermis. Pressure-sensitive afferents have been reported in the skeletal muscle and tendon of cats [4], and in humans, anesthetizing the skin has shown deep pressure sensation to predominantly originate from deeper tissues below the skin [3]. However, it is not yet known whether deep pressure is perceived in these deeper tissues (muscle and/or connective tissues) by A or C fibers (or a mix). We tested patients with sensory neuronopathy earlier this year and found that two (of two) patients lacking A-beta afferents were unable to perceive deep pressure at non-painful levels (Case & Liljencrantz et. al., manuscript under review). We therefore hypothesize that A-beta fibers underlie the perceived intensity of non-painful deep pressure.

Deep pressure touch, as in massage therapy, also frequently conveys a pleasant affective response. Deep pressure touch has been shown to reduce anxiety [5], pain, and unpleasant affect [6]. For the beneficial effects of massage therapy [7], 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 [8]. Deep pressure is a components of numerous complementary health techniques that significantly reduce depression, stress, and pain [9, 10]. This pleasant affective response may relate directly to the sensory input of deep pressure, analogous to the pleasantness evoked by stimulating C low-threshold mechanoreceptors (C-LTMRs). CLTMRs are a subtype of unmyelinated sensory afferents that respond optimally to slow gentle stroking of the skin; this type of

touch is typically perceived as pleasant ([11, 12]). C-LTMRS are thus often considered affective afferents. We hypothesize that the A-beta fibers innervating deeper tissues provide an affective input analogous to the skin's C-LTMR to sense pleasant deep pressure touch (as in massage therapy).

To isolate the role of different sensory fiber types in deep pressure perception, we will administer an ischemic-compression block, which involves inflating a blood pressure cuff to approximately 100mmHg above systolic blood pressure [3, 13]. This procedure has previously been used to separate the function of A and C fibers [3, 13]. As blood flow is cut off, large diameter (A) fibers are affected before small diameter (C) fibers. Sensations associated with A-beta fibers are lost, on average, around 20 minutes after placement of the block [3, 13]. By monitoring sensory ability over time, we can determine when A-beta fiber function has been lost and immediately test the intensity and pleasantness of deep pressure and light brushing to determine whether they depend predominantly on A-beta fibers. Testing of warm and cool thresholds will allow us to confirm the continued functioning of A-delta and C-fibers [14].

An ischemic nerve block typically causes some discomfort and/or pain due to the high intensity of cuff pressure. Pain and discomfort are typically focused at the site of the inflated cuff. Healthy adult participants are typically able to tolerate at least a half hour of nerve block, but some discontinue testing between 30-60 minutes due to pain or discomfort [13]). Feelings of anxiety and disgust are also common due to the loss of sensation from the arm. Testing of pleasant sensation may be affected by the painful context of the nerve block. Pleasant sensations may be more difficult to detect or perceive during the experience of pain or other aversive affective states. However, pleasant sensations still occur and can be quantified during painful experiences. For example, patients with chronic pain still rate C-LTMR touch as significantly pleasant [15]. Since all ratings will be compared between arms, the painful context will affect the two arms equally and thus should not affect any positive conclusions drawn from our outcome measures.

Elucidating the sensory mechanisms of non-painful deep pressure will help us understand how manual therapies create calming and pleasant sensations and understand more about the analgesic effects of deep pressure. This could help to strengthen therapeutic strategies for treatment of chronic pain.

2. Study Objectives

a. **Primary objective:**
Hypothesis: Participants will experience a significant decrease in the intensity of deep pressure after loss of A-beta-associated sensation due to ischemic-compression block.

b. **Secondary objectives**:
Hypothesis 1: Participants will experience a significant decrease in the pleasantness of deep pressure after loss of A-beta-associated sensation due to ischemic-compression block.
Hypothesis 2: Participants will experience a significant decrease in the intensity *but not* pleasantness of gentle brushing after loss of A-beta-associated sensation due to ischemic-compression block.

3. Subjects

a. Description of study populations

Based on our power calculations, we would like to have 12 healthy men and women who meet the inclusion/exclusion criteria described below participate in the study. Because of possible dropouts during the study due to discomfort of the nerve block, we will set our maximum accrual at 24 participants (see detailed explanation of sample size estimate on p. 21). 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. Fluent in English.

3. Able to provide written informed consent.
4. Enrolled in 16-AT-0077, "Clinical and Scientific Assessment of Pain and Painful Disorders"

c. Exclusion criteria

1. Unable to comply with study procedures.
2. Have used recreational drugs in the past 30 days.
3. Pregnancy or breastfeeding.
4. Congenital upper 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. 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).
7. Major medical condition, such as kidney, liver, cardiovascular (including blood clots, hypertension, preexisting cardiac arrhythmia, lymphadenopathy), autonomic, pulmonary, or neurological problems (e.g., seizure disorder) or a chronic systemic disease (e.g., diabetes) or Raynaud's disease.
8. Personal history or first-degree family history of blood clots or clotting and circulatory disorders
9. History of a seizures or first-degree family member with a seizure disorder
10. High (>140/90) or low (<90/60) blood pressure
11. Current and untreated diagnosis of major depression, post-traumatic stress syndrome, bipolar disorder, psychosis, anxiety or panic disorder, alcohol or substance use disorders
12. History of fainting with blood draws
13. Any medical counter-indications to the nerve blocks.
14. Participant's arm unable to fit in inflated arm blood pressure cuff

15. 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.
16. Used topical pain-relieving creams in the testing area within 24 hours of testing or non-steroidal anti-inflammatory drugs (NSAIDS), (e.g. aspirin, ibuprofen, acetaminophen, or naproxen) within 3 days of testing
17. Recent use of medications that increase risk of seizures (e.g. antidepressant Wellbutrin or antipsychotic Haldol)
18. NIH employees who are subordinates, relatives, or co-workers of the investigators, or NCCIH DIR employees.

Exclusion criteria for individual study session

1. 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 1: 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 1.

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 different sensory fibers in perceiving how touch feels. We will explain that participants will participate in a single session of about 2 hours in length. We will place an ischemic-compression

block with a tourniquet that will cut of blood flow to one arm, and then rate their perception of sensory stimuli on both arms. The purpose of the study is to identify the role of A-beta, A-delta, and C-fibers in the perception of deep pressure touch. 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.

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.

b. Recruitment

We anticipate recruiting up to 24 potential participants. Participants will be recruited from our currently active NCCIH Phenotyping protocol (16-AT-0077). 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. NCCIH employees cannot participate in this protocol. The anticipated accrual rate is approximately four participants per month. With the accrual ceiling set at 24 participants and expected rate of enrollment of 4 participants per month, it may take approximately 6 months to reach accrual target and another 12 months to complete data analysis for a total study duration of 18 months.

Telephone Interview (pre-screening)

A pre-screening telephone call of approximately 10 minutes will be conducted to determine eligibility (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 pre-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 the single study 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 will be accomplished under NCCIH protocol 16-AT-0077, and the following procedures will be performed to assess eligibility:

- Urine collection for pregnancy screening (within 24 hours of testing for participants who are able to become pregnant) and drug screening ("Drug Abuse Screen Qualitative, urine"; panel includes Amphetamines, Benzodiazepine, Opiates, Cocaine metabolites, and Cannabinoids).
- Physical exam and medical history (within one year of screening unless otherwise specified) to assess the following:
    - Congenital upper limb deficiency or amputation
    - Peripheral neuropathy
    - Dermatological conditions that would influence cutaneous sensitivity
    - Assessment of current medications and treatments including use of pain medications; topical pain relieving creams; and medications that increase risk of seizures
    - Major medical conditions including psychiatric conditions and alcohol or substance use disorders
    - History of clotting and circulatory disorders
    - History of seizures and seizure disorders
    - History of fainting with blood draws
    - Ability to fit in inflated arm blood pressure cuff

If deemed eligible, the participant will provide consent for the current protocol prior to performing any procedures specific to this protocol.

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 research session.

Consent will be obtained before any study procedures will be done. Once enrolled in the current protocol, a LHP will review eligibility criteria at the beginning of each session, to confirm that participants are eligible and meet day-of-study criteria.

d. Study procedures

Participants eligible to proceed will be asked to complete a single session, in the NIH Clinical Research Center.

An LHP will review eligibility criteria at the beginning of each session, to confirm that participants remain eligible and meet day-of-study criteria (5-10 minutes). Then, the nerve block procedure and sensory testing will be performed as depicted in **Figure 1. Study Flow** and described in detail below (approximately 1 hour, all procedures for research purposes):

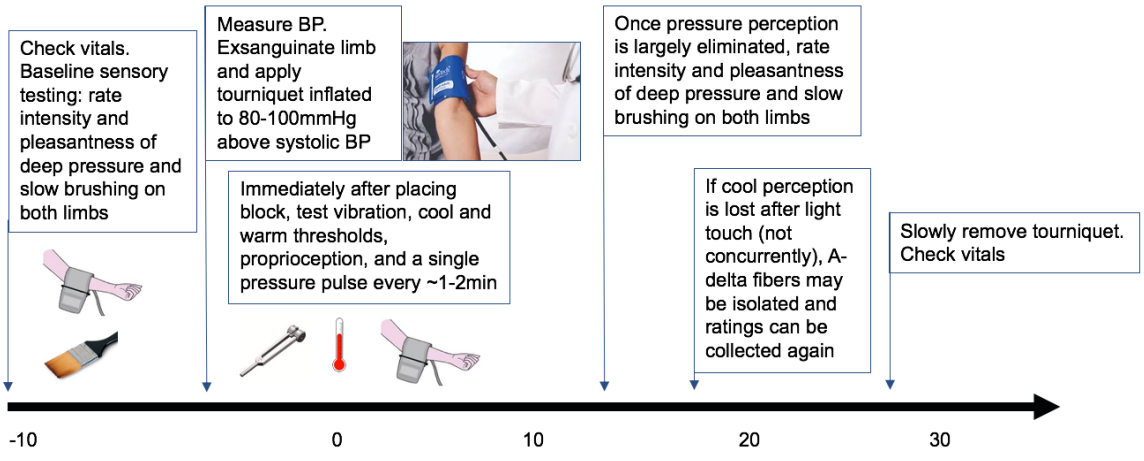

Figure 1. **Study Flow**

Each nerve block session will follow approximately the timeline shown. Timing is approximate as nerve blocks progress at different speeds for different individuals.

Baseline affective touch testing will be performed on both arms (ratings of the intensity and pleasantness of slow brushing and deep pressure). The tourniquet will be placed by a LHP. Sensory testing will be conducted regularly to monitor block progression and loss of A-beta-associated sensation. When A-beta associated perception has been substantively eliminated, ratings of slow brushing and deep pressure (affective touch) will be repeated on each arm/hand. Sensory monitoring will continue and affective ratings may be repeated if further A-beta or A-delta percepts are lost before C-fiber function (loss of warm perception; this separation is not always observed; [14]). Testing is likely to be completed within 30-40 minutes from block placement. The nerve block will be removed by 60 minutes from placement.

Details of Ischemic-compression nerve block

An ischemic-compression block (see **Figure 2** below) will be placed to eliminate A-beta associated sensation. Ischemic-compression blocks affect large myelinated fibers before unmyelinated fibers are affected [14]. The subject will hold one arm over their head for approximately one minute and the LHP will exsanguinate the arm. Half the subjects will be tested on the dominant arm and half on the non-dominant arm to avoid confounds in arm dominance and affective responses. The LHP will then inflate tourniquet to approximately 100mmHg above the subject's systolic blood pressure (BP) (e.g. [13, 14]). The subject will then rest their arm comfortably on a pillow on a table placed in front of them. Sensory testing will be conducted with sight occluded and white noise or similar sounds via headphones to eliminate visual and auditory cues in the sensory tasks.

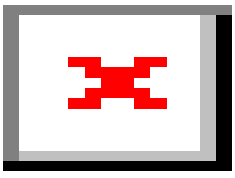

Figure 2. An ischemic-compression block

Details of Sensory testing paradigm

Ratings of intensity and pleasantness of pressure and brushing: At baseline and after loss of sensation associated with A fibers, perception of deep pressure and gentle brushing will be tested on both arms. Deep pressure will be administered to the hand and wrist for approximately 20 seconds using a hand massager that applies oscillating pressure. Gentle brushing will be administered to the hand/forearm by a trained experimenter at a rate of approximately 3cm/second for approximately 15 seconds. Participants will rate intensity and pleasantness of each sensation on VAS scales with anchors of "no sensation" to "highest possible intensity" and from "extremely unpleasant" to "neutral" (midpoint) to "extremely pleasant." Nearly identical VAS scales have been successfully used in our lab in numerous previous studies to distinguish the intensity versus pleasantness of sensory stimuli (e.g. [16, 17]). If cool perception is lost after light touch (not concurrently), A-delta fibers may be isolated and ratings can be collected again. Loss of cool and light touch often coincide, however [14]. Ratings of bad mood and anxiety will also be collected. They will be rated verbally on 0-10 scales (0 = none; 10 = worst you have experienced).

After placement of the tourniquet but before elimination of A-beta associated sensation, sensory testing will be conducted to monitor the block progression. Sensory testing will be conducted nearly continuously, which each test conducted approximately every ~1-2 minutes. All testing will be conducted distal to the block. The tests conducted during sensory monitoring may include the following:

Vibration perception (A-beta): A custom vibration device administering ~200 Hz vibration to the skin of the palm will be set for a random duration between 1-6 seconds. Participants will press a button (or similar response) when they perceive the onset and offset of the vibration.

Warm (C-fiber) and cool (A-delta) perception: Heat stimuli will be administered by the trained experimenter to the ventral surface of the forearm or palm using a contact

thermode (Medoc Pathway System; Medoc Ltd., Advanced Medical System, Israel). The Medoc thermode is used in accord with its FDA approved indication of human pain reception and transmission of sensory pathways. Warm threshold will start at approximately 32 °C and increase until the participant responds with a button press, eventually stopping at 50 °C. Cool threshold will similarly start at approximately 32 °C and decrease until the participants indicates perception of the cool, or to 0 °C. These threshold procedures are standard thermal testing procedures and have been used in our lab and elsewhere, including in currently approved NIH protocols [18].

Pinprick perception (A-delta): A pinprick (superficial; does not break skin) will be administered each test cycle and reaction time will be collected by a button press (or similar response).

Proprioception (A-alpha and A-beta): The experimenter and/or participant will move one finger up or down and the participant will indicate which direction the finger was moved in.

Pressure (unknown sensory afferent type): A quick pulse of pressure will be administered via a pressure algometric device The participants indicate if they detected a pressure change and/or rate the intensity of the sensation from 0-10.

NRS ratings of current ongoing pain and discomfort (0-10) will be collected. 0 = no pain/ no discomfort and 10 = intolerable pain or discomfort.

c. End of participation

Participation will be completed upon completion of the procedures described above. Because participants are healthy volunteers, the only information to be shared with participants 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. 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 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 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 collaborators on this study, Hakan Olausson (Linkoping University, Sweden) and Jaquette Liljencrantz (Sahlgrenska Academy at University of Gothenburg).

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 will be 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.
    - Demographic data (age and sex) and behavioral data such as performance on a task, may also be shared. As this protocol concerns studies healthy volunteers, 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

None

7. Risks and Discomforts

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 associated with ischemic-compression nerve block:

Ischemic-compression blocks are considered safe when administered for under 2 hours at 250 mmHg in adults, including in elderly adults and in patients with medical comorbidities [19]. Complications are rare and arise most often observed the use of tourniquets during surgical procedures, in patients with medical conditions [20]. Ischemic-compression blocks have been used in several experimental studies of sensory perception without any reported adverse effects [3, 13, 21]. Participants are not always able to tolerate the block for a full session due to pain or discomfort at the site of the blood pressure cuff (e.g. in one study a number of participants ended their 1-hour session early due to pain or discomfort, but all subjects tolerated a minimum of 27 minutes [13]). Vasovagal responses are another possible side effect due to anxiety or changes in blood pressure. Punctate hemorrhage of the skin or shearing of the skin are other minor risks. When the cuff is released, painful paresthesia may occur [22]. By releasing the pressure very slowly (e.g. over the course of more than a minute), as we will in the current study,

we have found that paresthesia is minimized and does not cause more than very mild discomfort.

There is a risk of inducing a seizure due to blood pressure changes in an individual with a history of seizure disorder, so these individuals will be excluded. In addition, due to the theoretic risk of deep vein thrombosis (evidence for this risk is mixed; [20, 23]), individuals with a first-degree family history of blood clots, clotting or circulatory disorders will be excluded.

Nerve injury and swelling, metabolic dysfunction, and muscle injury are possible but rare effects of prolonged compression during prolonged surgical procedures [23]. Therefore, we will minimize compression time, releasing the cuff within 1 hour, and monitor the subject for any adverse physical or psychological responses. These side effects have not been reported to our knowledge during short-duration experimental procedures. Participants will be screened and excluded for cardiovascular disease, or drugs that can produce adverse cardiovascular effects. The investigators will closely monitor subjects during each study session for any signs of nausea or discomfort. In the case of an acute adverse event, medical evaluation and treatment recommendations will be provided by the LHPs on this protocol. 911 will be called if immediate treatment is required. Participants are to be referred to their local physician if further evaluation or treatment is necessary. Participants will be followed weekly by a phone call until resolution of AE's.

Risks and discomforts associated with heat and cool stimuli

The nature of the study requires the application of warm and cool stimuli that can become painfully hot or cold if not perceived at typical thresholds. However, these stimuli have been used in previous studies, have proven to be easily tolerated, and do not cause permanent tissue damage. Slight reddening or darkening of the skin may occur. This is transient and disappears after termination of the testing. Heat pain stimulation has been used extensively without any long-term adverse effects [17, 18, 24].

Risks and discomforts associated with vibration, pinprick, and compression stimuli

There are no known risks of the vibration or pinprick stimuli other than possible minor discomfort. Pressure stimuli may be uncomfortable to some participants, but the pressure will be lower than a standard blood pressure cuff and familiar to all participants. Repeated inflation could dislodge any active blood clots in the participant's arm, so all participants will be checked during medical screening to ensure they do not have any clinical signs of clots present.

8. Subject Safety Monitoring

Participants will be monitored by the study investigators during the study visit for study outcomes and adverse events. All subjects will be instructed about, and receive practice with, all sensory testing before it is administered, and adequate comprehension of the instructions for each test will be insured by the test examiner.

During the nerve block, at least one experimenter will remain in the room with the subject at all times. A LHP will be in the clinic at all times available for consultation. The participant's vital signs will be checked before and after the nerve block. Study staff will monitor subjects during participation and subjects will be encouraged to tell experimenters of any discomfort or concerns. If apparatus, etc., cannot be adjusted to relieve discomfort that the subject cannot tolerate, the experiment will be stopped. Subjects may withdraw at any time.

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; 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. Participants who terminate early because of not tolerating the block well will not be rescheduled.

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, individual subject sessions will be stopped if requested by participants or if the investigators feel it is in the best interest of the participant.

9. Outcome Measures

Primary outcome measures

The primary outcome is the change or difference score (pre to post) in intensity ratings of deep pressure measured before and after loss of A-beta-associated sensations on the affected arm versus the unaffected arm (e.g. compared between arms by a paired t-test at the group level).

Secondary outcome measures

The secondary outcomes include change or differences in pleasantness ratings of deep pressure or intensity or pleasantness ratings of slow brushing and fast brushing before and after loss of A-beta and A-delta-associated sensory function (relative to unaffected arm).

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 or equivalent nonparametric test to evaluate the effect of the nerve block

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 12 healthy participants. G*Power (http://www.gpower.hhu.de) was used to compute the necessary sample size. In our recent study of deep pressure perception (manuscript in preparation; data available upon request), the same oscillating deep pressure sequence was rated as an intensity $M = 4.2$ (scaled to our 0-10 scale); we expect intensity to drop at least 2 points on our 0-10 rating scale (likely more since patients lacking A-beta fibers had no perception of deep pressure in our previous study, Case & Liljencrantz et. al., under review). In our previous study healthy participants rated the same deep pressure sequence on two different days and the standard deviation of the change in their rating from Day 1 to Day 2 was 1.7. Based on a

2-point change (due to blocking A-beta fibers which should fully eliminate sensation) and a standard deviation for within-subject rating change scores of 1.7, we expect a Cohen's effect size $d = 1.17$. Setting statistical power to 95% and Type I error probability to $\alpha=0.05$, 12 subjects would be required to complete the study. We expect up to a 50% dropout rate of participants based on prior NIH studies and the discomfort of prolonged nerve blocks found in other studies [13]. Thus, we will enroll up to 24 participants and dropouts will be replaced.

11. Human Subjects Protection

a. Subject selection

Accrual will be equitable among the participants eligible for this study.
We are excluding people over 50 years of age because older adults have elevated pain thresholds for brief pain stimuli [27] and there is no evidence that their discriminative functions are unchanged.

b. Justification for exclusion of children

The current study constitutes initial research into the sensory mechanisms underlying deep pressure touch and involves an ischemic compression block which is a procedure likely to not be well tolerated by children, with no particular benefit to them. Results are very likely to generalize to children since the role of sensory afferents is consistent across the lifetime. To confirm this a separate, age-specific study in children would be 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 clear, rapid and direct communication is needed with all members of the study team, due to the rapid progression of the nerve block. Further, VAS rating scales we will use have not been validated in languages other than 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 [25, 26], and because nerve blocks may cause vasovagal responses that could affect a developing fetus.

We are excluding individuals who work at NIH and are subordinates, relatives, or co-workers of the investigators, or NCCIH DIR employees. Other NIH staff may participate.

d. Justification for sensitive procedures

N/A

e. Safeguards for vulnerable populations and sensitive procedures

Pregnant women will be excluded from participation due to the unknown risks of performing a nerve block and altering blood pressure on the developing fetus. A pregnancy test will be conducted to protect against the inclusion of a pregnant woman. 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 but is likely to yield generalizable knowledge about the perception of deep pressure, 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 the study session, after the initial inclusion criteria have been met via the telephone interview, physical exam (conducted under protocol 16-AT-0077), and drug and pregnancy tests (conducted under protocol 16-AT-0077), but prior to 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 entire study will halt until the plan to address the SAE has been developed by the investigator, clinical director, and the IRB and SAE has resolved,.

16. Quality Assurance (QA)

a. Quality assurance monitor

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

b. Quality assurance plan

At least annually, 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 SOP. This study is classified as “minimal risk” and thus will undergo random audits. 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. Non-NIH investigators will abide by the conflict-of-interest policies of their own institutions.

c. Role of a commercial company or sponsor

N/A

22. Technology Transfer

No technology transfer agreement is required for this protocol per communication with a local technology transfer office. Agreements will be put in place if they become necessary.

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:

Study session (sensory testing with nerve block)	$150 for clinical screening, sensory testing, and nerve block, up to 2 hours.
Overtime (Session lasts more than 2 hours due to delays with urine tests or other delays caused by staff or equipment)	$50 per hour up to 2 additional hours.
Maximum total compensation	$250

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25. Attachments/Appendices

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

Protocol T-AT-0345_____ 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 a new study we have on the role of different sensory fibers in touch perception? 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 different sensory fibers in perceiving types of touch sensations. If you are eligible and choose to participate, you will be scheduled for a single test session. This session would last approximately 2 hours. During the session you would have a brief medical exam and provide a urine sample for a drug test (and pregnancy test). Then, you would be seated in an exam room and complete some sensory testing such as detecting or rating brushing, vibration, warm sensation, cool sensation, movement, pinprick (that does not pierce the skin), or pressure on your arm or hand. Next, we would take your blood pressure and inflated a blood pressure cuff to approximately 100mmHg above your systolic BP. This causes blood flow to be cut off to your arm and will cause you to slowly lose different sensations over the course of the testing period. The sensations will return to normal after the blood pressure cuff is removed at the end of the session. While it is inflated, we will do sensory testing almost continuously to track your sensations over time as different nerve fibers become affected. The nerve block will be removed most likely by 40 minutes, or by 1 hour at the very most. After your sensation has returned to normal you will be free to leave. You will be asked to wear short sleeves or change into scrubs for each session in order to access the full arm.

There is no pain testing in this study except for the pinprick, which is a bit like a mechanical pencil- it does not penetrate the skin. However, having the blood pressure cuff inflated to cut of blood flow can cause pain or discomfort, as well as emotions of disgust in response to the limb turning pale or losing sensation. We will try our best to keep you comfortable and keep your limb covered so you are not looking at it. You may choose to end the testing early if it is not tolerable. During the sensory testing, you will experience light touch with a soft brush, a hand massager, vibration, pinprick, pressure with an inflatable arm compression sleeve, warm and cool pain sensations using a thermode, and gentle movement of your fingers.

There are no risks of our sensory testing. The risks of the nerve block (blood pressure cuff block) aremostly pain or discomfort, or the emotional response to feeling the temporary loss of sensation. However, an uncommon side effect is a vasovagal response like vomiting or fainting. If you have history of a seizure it could induce a seizure, so we would exclude you. Finally, we would exclude you if you have a history of blood clots or circulatory problems in yourself or your family, due to a rare risk of dislodging blood clots or damaging nerves.

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 the nerve block has any negative effects for a developing fetus.

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

VERIFYING EXCLUSION CRITERIA

CRITERIA	ANSWER	EXCLUDE IF
Enrolled in 16-AT-0077 (confirmed by experimenter)	□ YES □ NO	NO
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
Do you have a congenital upper limb (arm) deficiency or amputation of an arm?	□ YES □ NO	YES
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
Do you have a chronic disease (e.g. diabetes) or a major medical condition such as kidney, liver, pulmonary, autonomic,	□ YES □ NO	YES

cardiovascular (e.g. blood clots, hypertension, preexisting cardiac arrhythmia), or neurological disease (e.g., seizure disorder)?		
Have you ever had a blood clot or a clotting disorder, or has anyone in your first-degree family?	□ YES □ NO	YES
Have you ever had a seizure or do you have a first-degree family member with a seizure disorder?	□ YES □ NO	YES
Have you been diagnosed with high blood pressure (hypertension) or low pressure (hypotension)?	□ YES □ NO	YES
Have you had or do you currently have a diagnosis of major depression, post-traumatic stress syndrome, bipolar disorder, psychosis, anxiety or panic disorder, alcohol or substance use disorders? If so, is it treated with medication? Or are you currently taking medication for any of those conditions?	□ YES □ NO	YES (if current and untreated/ unstable)
Have you ever fainted from a blood draw? More than once? (Discuss with medical team)	□ YES □ NO	YES
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

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 $150, $50 per hour for additional delays
☐	Explained transportation	Transportation will not be reimbursed but free parking is available (validation).
☐	Updated enrollment log and assigned subject code	

SCHEDULE SESSION _____; Time: _____
REMINDER: If you 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 or participants who exhibit signs of intoxication or alcohol withdrawal syndrome will be excluded without a chance to reschedule, 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	POS
Is the participant showing behavioral signs of intoxication? • Speech: overly talkative, argumentative, opinionated or interrupting; stumbling over words; loud, inappropriate language or jokes	□ YES □ NO	YES

• 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		
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

Attachment 2: Precis for clinicaltrials.gov

Précis:

Objective: Our sense of touch includes the intensity, pleasantness and unpleasantness of touch. We are investigating the sensory fibers that convey these various aspects of touch sensation. The current study will examine the role of unmyelinated sensory fibers in the perception of several types of touch to the arm.

Study Population: Up to 24 healthy participants will be enrolled in the study.

Design: Participants will receive baseline sensory testing including perception of hot and cold temperatures, vibration, pressure, and gentle brushing touch. Then, a tourniquet (blood pressure cuff) will be inflated to cut of blood flow to one arm. This will test the role of certain sensory fibers in several different touch sensations. Sensory testing will continue for a maximum of 1 hour. Then, the nerve block will be released. Ratings of mood, anxiety, pain, discomfort, intensity, and pleasantness/unpleasantness will be collected throughout the study session.

Outcome measures: We will compare subjective ratings (including intensity and unpleasantness/pleasantness) before and after the nerve block on the blocked and unblocked arm to determine the role of unmyelinated and myelinated sensory fibers in the perception of light touch and deep pressure.

26. Consent Forms

Please see separate Consent Form document.