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Assessing peripheral fibers, pain sensitivity, central sensitization, and descending inhibition in Native Americans: main findings from the Oklahoma Study of Native American Pain Risk (OK-SNAP)

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Abstract

Native Americans (NAs) have a higher prevalence of chronic pain than other U.S. racial/ethnic groups, but there have been few attempts to understand the mechanisms of this pain disparity. This study used a comprehensive battery of laboratory tasks to assess peripheral fiber function (cool/warm detection thresholds), pain sensitivity (eg, thresholds/tolerances), central sensitization (eg, temporal summation), and pain inhibition (conditioned pain modulation) in healthy, pain-free adults (N=155 NAs, N=150 non-Hispanic Whites, NHW). Multiple pain stimulus modalities were used (eg, cold, heat, pressure, ischemic, electric), and subjective (eg, pain ratings, pain tolerance) and physiological (eg, nociceptive flexion reflex) outcomes were measured. There were no group differences on any measure, except that NAs had lower cold pressor pain thresholds and tolerances, indicating greater pain sensitivity than NHWs. These findings suggest that there are no group differences between healthy NAs and NHWs on peripheral fiber function, central sensitization, or central pain inhibition, but NAs may have greater sensitivity to cold pain. Future studies are needed to examine potential within-group factors that might contribute to NA pain risk.

Keywords

quantitative sensory testing; ethnic differences; Native Americans; pain inhibition; nociceptive flexion reflex; central sensitization

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1.0 Introduction

Native Americans (NAs) have a higher prevalence of chronic pain than other U.S. minorities and non-Hispanic Whites (NHWs)[4;42;100]. Unfortunately, there is a lack of research that attempts to understand the mechanisms for this pain disparity. Most studies have focused only on pain prevalence, finding that arthritis[34;57] back pain[4;27], headaches[72], and dental pain[49] are among some of the chronic pain conditions that have the highest prevalence in NAs. Given that chronic pain results in tremendous health care utilization, economic burden, disability, and loss of productivity[51], the mechanisms contributing to this pain disparity must be understood.

Previously, we conducted a small pilot study of healthy, pain-free NAs and NHWs and found that NAs were *less* pain sensitive (eg, *higher* pain tolerance) and showed *reduced* central sensitization on a physiological marker of spinal nociception (eg, lower temporal summation of the nociceptive flexion reflex, TS-NFR)[65]. These findings suggested that risk factors for chronic pain may be different for NAs than other minorities, because the opposite findings had been noted in African-Americans and Hispanics[15;18;20;31;32;61;62;84;103;109;113]. We argued that, since pain is normally adaptive, chronically dampened pain in NAs (lower tolerances, reduced spinal cord excitability) may lead to difficulties detecting physical harm, protecting oneself from injuries, and learning to avoid future dangers[23;25;96]. Moreover, chronic activation of descending inhibition could exhaust the capacity to inhibit pain, perhaps through disruption of the opioid system[8-10;58].

Conditioned pain modulation (CPM) is the traditional method to assess CNS inhibition in the laboratory. Although we did not assess CPM in our pilot study, we did assess emotional modulation of pain and found that NAs were less able to facilitate (disinhibit) pain during negative emotions[64]. We hypothesized this might be due to chronic over-activation of CNS inhibition. Thus, when taken together, chronic pain risk in NAs could be due to problems detecting physical harm (low pain sensitivity) and/or over-activation of inhibitory mechanisms that reduce spinal excitability (but might ultimately deplete inhibitory resources).

The current study was designed to replicate and extend our small pilot study to a larger sample of NAs and NHWs using a wider array of assessment methods. Pain/nociception measurement tasks were chosen to assess differences in pain sensitivity (eg, pain threshold/tolerance), central sensitization (eg., TS-NFR, TS-pain), and CNS pain inhibition (eg, CPM). Thermal detection thresholds (ie, cool/warm thresholds) were also used to evaluate peripheral nociceptive fiber function. Outcomes included both subjective (eg, pain response) and physiological (eg, TS-NFR, CPM of NFR) targets. To rule out potential confounds, care was taken to ensure groups were similar on important background variables or statistically controlled. Moreover, only healthy, pain-free participants were recruited to help ensure that any observed differences in pain processing were not due to disparities in disease severity and/or pain treatment[21;59;97]. Based on our pilot data, we hypothesized that, relative to NHWs, NAs would exhibit: 1) reduced pain sensitivity, 2) reduced central sensitization, and 3) increased CNS inhibition.

2.0 Materials and Methods

2.1 Participants

2.1.1 Sample Size Determination.—Power analyses conducted in G*Power (version 3.1.9.2) were based on effect sizes derived from our pilot study of pain processing in NAs[65], as well as effect sizes for race/ethnic differences in CPM from Campbell et al[16]. These analyses suggested that 120 per group ($N=240$ total) would result in power of 0.80 for most of the outcomes used in the current study (power=.80 for effect sizes $d=.36$) at $\alpha=.05$. So, $N=240$ was the targeted sample.

2.1.2 Recruitment and Inclusion/Exclusion Criteria.—These data were collected from the Oklahoma Study of Native American Pain Risk (OK-SNAP). Healthy, pain-free participants were recruited from newspaper ads, tribal newspapers, fliers, personal communications with NA groups, email announcements, and online platforms (e.g., Facebook). Potentially eligible participants were invited to attend the first laboratory testing day, which began with a thorough screening for inclusion/exclusion criteria. Participants were excluded for: 1) <18 years old, 2) history of cardiovascular, neuroendocrine, musculoskeletal, neurological disorders, 3) chronic pain or current acute pain problems, 4) BMI ≥ 35 (due to difficulties recording electromyogram for NFR), 5) use of anti-depressants, anxiolytic, analgesic, stimulant, or anti-hypertensive medication, 6) current psychotic symptoms (assessed by Psychosis Screening Questionnaire[7]) or substance use problems, and/or 7) an inability to read and speak English. Data collection occurred between March 2014 and October 2018. The study was approved by Institutional Review Boards of The University of Tulsa, Cherokee Nation, and the Indian Health Service Oklahoma City Area Office. NA status was verified from Certificate of Degree of Indian Blood or tribal membership cards. Participants were given an overview of all procedures and told they could withdraw at any time. All participants provided verbal and written informed consent prior to enrollment and received a \$100 honorarium for the completion of each testing day (or \$10/hour for non-completed days).

2.1.3 Final Sample.—A total of 391 participants were screened for the study, but 62 did not meet inclusion criteria. Of the 329 who were eligible to participate, 247 completed both testing days, 41 completed only one day, and 39 completed part of one testing day. Two participants' data were lost due to a computer malfunction. 22 participants were non-NA minorities and thus were excluded from the current analyses. Thus, the final sample of participants who could contribute at least partial data was 155 NA (64 males) and 150 NHW (76 males). Table 1 provides characteristics of these participants. NA participants in the current study represent tribal nations predominately from the southern plains and eastern Oklahoma tribes.

2.2 General Overview of Procedures/Testing

Testing was conducted over a 2-day period, each lasting 4-6 hours (Fig 1). Informed consent and inclusion/exclusion screening were conducted on the first day, followed by a brief semi-structured interview about the meaning of pain (data presented elsewhere). On one of the testing days (referred to here as Pain Sensitivity Day) the following tests were administered:

cool and warm thresholds, heat pain threshold/tolerance, mechanical pressure pain threshold, stimulus-response to heat, temporal summation of heat pain, cold pressor pain threshold/tolerance, and ischemia pain threshold/tolerance. On the other testing day (referred to here as Pain Modulation Day) the following tests were administered: NFR threshold, Pain30 threshold (if necessary), temporal summation of NFR threshold, 52°C heat pulse series, single electric stimulations, temporal summation of NFR and electric pain, sham CPM (no conditioning stimulus presented, see description below), CPM (which includes 2-min 10°C cold water conditioning stimulus), and emotional controls of nociception (ECON; data not presented). Order of testing day was counterbalanced, blocking for race and sex. Moreover, tests within each day were partly randomized (see Fig 1). Breaks were provided between tasks to minimize carryover. Several questionnaires were administered on each testing day at the beginning and during breaks to assess background characteristics and control variables.

2.3 Background Questionnaires and Control Variables

These questionnaires were administered to assess eligibility (eg, Demographic and Health Status) and to examine whether groups differed on important background characteristics.

2.3.1 Demographics and Health Exclusion.—A custom-built demographic and health status questionnaire was used to obtain standard background information, as well as information regarding health problems. It was administered immediately following informed consent. The questionnaire asked about: age, sex, marital status, education level, employment, and income level, as well as potential exclusionary criteria such as cardiovascular problems, neurological problems, chronic pain, and medication use. Weight and height were assessed from a medical scale to calculate body mass index (BMI).

2.3.2 Blood Pressure (BP) and Resting Heart Rate (HR).—A medical grade device (Dinamap; Tampa, FL) was used to measure resting systolic BP, diastolic BP, mean arterial pressure (MAP), and HR 3 times at the beginning of each testing session (3 min inter-test interval) while the participants sat comfortably in the recliner with their arm resting on the arm of the chair. The average of each variable from the first testing day is reported.

2.3.3 Traditional (Dispositional) Pain Catastrophizing.—The 13-item Pain Catastrophizing Scale (PCS)[93] was used to assess dispositional catastrophizing at the beginning of testing to assess how each participant generally reacts to painful events. This was done to establish whether groups generally differed in pain catastrophizing. Scores ranged from 0 to 52, with higher scores indicating greater catastrophic thoughts.

2.3.4 Current Affect.—Positive and negative affect prior to testing were assessed from the Positive and Negative Affect Schedule (PANAS)[106]. Each positive and negative affect subscale consists of 10 items that measure positive and negative emotions, with subscales ranging from 10 to 50. Higher scores on each scale indicate greater positive or negative affect.

2.3.5 State Anxiety.—State anxiety prior to testing was assessed by the 20-item state anxiety subscale of the State Trait Anxiety Inventory (STAI)[87]. The subscale ranges from 20-80, with higher scores indicating greater current anxiety.

2.3.6 Sleep Quality.—The perceived sleep quality item from the Pittsburgh Sleep Quality Index (PSQI) was used to assess differences in sleep [13]. The item ranges from 0 (very good) to 3 (very bad), thus higher scores represent poorer sleep.

2.3.7 Perceived Stress.—The Perceived Stress Scale (PSS) is a 10-item measure that assesses psychological stress within the past month. Scores range from 0-40, with higher scores indicating more perceived stress [22].

2.3.8 Psychological Distress.—The Symptom Checklist-90-Revised (SCL-90-R) was used to assess general psychological functioning [26]. The scale consists of 90 items that assess various psychological symptoms (eg, somatization, obsessive-compulsive, depression, phobic anxiety, paranoia). The Global Severity Index (GSI) of the SCL-90-R was used to assess overall psychological distress. Total GSI scores range from 0 to 4 with higher scores indicating greater distress.

2.3.9 Health Perceptions.—The General Health Perceptions subscale of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[105] was used to assess perceptions of physical health. The Bodily Pain subscale was used to assess the degree of pain and interference due to pain that has occurred over the past 4 weeks (prior to the first testing day). For both scales, scores are standardized to range from 0 to 100, with higher scores indicating better physical functioning.

2.4 Testing Environment

Questionnaires were presented by a computer with dual monitor capacity. Custom built LabVIEW software (National Instruments, Austin, TX) was used to control timing and order of the experimental protocol. One computer monitor was used by the experimenter to monitor experimental timing and physiological signals, whereas the second monitor was used by the participant to complete electronic questionnaires and to make ratings of stimuli. In order to reduce experimenter influences on testing, all reported experimental outcomes (except pressure pain) were conducted with participants in a sound attenuated and electrically shielded testing room while experimenters monitored the testing from an adjacent control room via a video camera (with a microphone) connected to a flat panel monitor. Participants wore a pair of sound attenuating headphones that allowed them to hear the experimenter and the computer-recorded instructions for each task.

During all tasks, participants were seated in a comfortable reclining chair (Perfect Chair Zero Gravity Recliner, Human Touch, Long Beach, CA) that kept their leg and hip angles constant for NFR testing. All heat stimuli were delivered using a Medoc (Haifa, Israel) Pathway device with a Contact Heat Evoked Potential Stimulator (CHEPS) thermode. The maximum intensity of any heat stimulus was set to 52°C (51°C for heat tolerance).

A circulating water bath (Thermo Fisher Scientific, Pittsburgh, PA) was used to assess cold pain threshold/tolerance and as the painful conditioning stimulus in the CPM task. Participants were asked to submerge their hand and forearm into the water bath and keep their fingers spread apart. The water level was kept constant (6" deep) across all participants to keep procedures standardized and maintain similar cold exposure to participants' hands/forearms.

To measure responses to mechanical pressure, a Medoc-Wagner computerized algometer was used (Haifa, Israel) and all experimenters were trained to use the software to maintain a constant rate of pressure increase while assessing pain thresholds.

Electric stimuli were delivered by attaching a bipolar electrode (Nicolet; 30 mm inter-electrode distance) filled with a conductive gel (EC60, Grass Technologies) over the retromalleolar surface of the left ankle after the skin had been cleaned with alcohol and abraded with an exfoliating cream (NuPrep, Weaver and Company, Aurora, CO). Stimulations were delivered by an isolated, constant current stimulator (Digitimer DS7A; Hertfordshire, England). Each stimulus consisted of a train of five 1 ms rectangular wave pulses with a 3 ms inter-pulse interval (250 Hz); however, the train was always experienced as a single stimulation. The maximum stimulation intensity was set at 50-mA to ensure safety.

2.5 Measurement of Peripheral Fibers

Cool detection thresholds were used to assess A δ fiber function[86;114], whereas warm detection thresholds were used to assess C-fiber function[66;85;101;102]. For both tasks, the CHEPS thermode was attached to the participants' left volar forearm using a Velcro strap and 5 trials were administered (1 practice, 4 trials averaged). Cool detection started at a baseline of 30°C and decreased at 0.5°C/s until the participant indicated that they perceived a cool sensation by making a button press. Warm detection was similar, except that the temperature started at 30°C and increased at 0.5°C/s until the participant indicated that they perceived a warm sensation. There was a random (25-35 s) inter-trial interval for both procedures.

2.6 Measures of Pain Sensitivity

Prior to pain sensitivity tests, participants were instructed on the difference between pain threshold and pain tolerance. Pain sensitivity was assessed from multiple stimulus modalities representing cutaneous thermal pain (heat pain threshold/tolerance, stimulus-response curve to heat, heat pain₄₅, cold pressor threshold/tolerance, 52°C heat series, 2-min 10°C cold water), deep tissue mechanical (pressure pain thresholds) and ischemic (ischemia pain threshold/tolerance) pain, as well as electric pain threshold/tolerance.

2.6.1 Heat Pain Threshold/Tolerance.—To assess heat thresholds and tolerances, the CHEPs thermode was attached to the participants' left volar forearm using a Velcro strap and heat pain threshold/tolerance were each assessed 5 times (1 practice, 4 averaged trials) [15]. Each trial started from a baseline of 32°C and heated at a rate of 0.5°C/s until the participant terminated the stimulus by pushing a button as soon as the heat became painful

(threshold) or intolerable (tolerance). There was a 25-35 s randomly determined inter-trial interval. In between tolerance trials, the thermode was moved slightly to avoid sensitization before the inter-trial interval was started.

2.6.2 Heat Stimulus-Response Curve.—To assess responses to non-painful and painful heat, 11 different heat pulses (40°C - 50°C) were delivered to the left volar forearm. Each pulse started at a 35 °C baseline, reached the peak temp in 0.5-s, held the peak temperature for 0.5-s, and then returned to baseline in 0.5-s. After each pulse, participants made a rating using a computerized numerical rating scale (NRS) with the following labels: 0 (no sensation), 10 (warm), 20 (a barely painful sensation), 30 (very weak pain), 40 (weak pain), 50 (moderate pain), 60 (slightly strong pain), 70 (strong pain), 80 (very strong pain), 90 (nearly intolerable pain), and 100 (intolerable pain). After the rating was made, there was a 20-30 s random inter-trial interval. The order of the 11 temperatures was randomized. After all 11 temperatures were administered, there was a short break, the thermode was moved slightly, and then the 11 randomized pulses were delivered again using the same procedures. The 2 ratings of each temperature were averaged to generate the stimulus-response curve.

2.6.3 Heat Pain45.—The 11 temperatures and the pain ratings from the stimulus response curve describe above were used in a regression equation to determine the temperature corresponding to a rating of 45 on the NRS (Heat Pain45). This individually calibrated temperature was used as a measure of pain sensitivity, but also as the suprathreshold stimulus intensity to assess temporal summation of heat pain (TS-Heat Pain) described below.

2.6.4 Cold Pressor Pain Threshold/Tolerance.—Participants were asked to submerge their hand and forearm into the circulating water bath that was held at $6 \pm 0.1^\circ\text{C}$ [15;60;73]. During the task, participants made continuous ratings on a computer-presented visual analog scale (VAS) ranging from “no pain” to “maximum tolerable pain.” These ratings were converted in real time to scores ranging between 0 and 100. The computer tracked the time following hand/forearm immersion. The time taken to reach a rating of 30 was defined as pain threshold and the time to reach a rating of 100 was defined as pain tolerance. The maximum cold water exposure was set to 5 min, but the participant was not informed of the limit.

2.6.5 Pressure Pain Threshold.—Pressure pain threshold was assessed at 3 body sites (masseter muscle, trapezius muscle, thumbnail), with site order randomized[70]. Pressure stimuli were applied by an experimenter by following the Medoc software to achieve an increase in pressure at a rate of 98 kPa/s. Participants were instructed to push a button as soon as they experienced pain. Up to 5 trials at each site were administered, and pressure pain threshold was defined as the average of the 3 best trials (determined by the accuracy of the experimenter’s pressure rate increase).

2.6.6 Ischemia Pain Threshold/Tolerance.—A standard forearm tourniquet test was employed to measure ischemia pain[36]. First, participants used their non-dominant hand to conduct hand exercises with a dynamometer (Lafayette Hand Dynamometer, Lafayette

Instrument Company, IN) at 50% grip strength for 2 min (1x/sec). Immediately after, the arm was raised for 15 s to allow for desanguination, then a blood pressure cuff was inflated to 220 mmHg around the biceps to occlude blood flow to the forearm. Participants were instructed to keep their arm still during the task. During occlusion, participants continuously rated their pain on the same VAS used during the cold pressor task. Similarly, the computer recorded the time taken to achieve to a rating of 30 (pain threshold) and 100 (pain tolerance). Maximum ischemia exposure was 25 min, but the participant was not informed of the limit.

2.6.7 Electric Pain Tolerance.—Electric pain tolerance was assessed using a single ascending staircase of stimulations that started at 0 mA and increased in 2 mA steps[75]. After each stimulus, the participant rated their pain on the same VAS used during the cold pressor. The stimulation intensity was increased until the participant rated the stimulus as the maximum tolerable pain. The computer recorded the stimulation intensity (in mA) corresponding to a pain rating of 30 (pain threshold) and 100 (pain tolerance).

2.6.8 52°C Heat Series.—6 blocks of 5 heat pulses (random 8-12 s inter-stimulus interval) were delivered to the left volar forearm. Each pulse started at a baseline of 32°C and increased to 52°C at a rate of 70°C/s and then returned to baseline at a rate of 40°C/s [39]. Each 65 s block of 5 pulses was separated by a short (~1 min) break during which the experimenter moved the thermode slightly. The first 5 blocks were used to assess contact heat evoked potentials from EEG (data to be presented elsewhere), so participants had their eyes closed [39]. The 6th block was used to assess pain sensitivity in response to the heat; therefore, immediately after each heat pulse participants rated their pain on the same computerized VAS used during the cold pressor task. The current study focused only on these pain intensity ratings as a measure of suprathreshold pain sensitivity.

2.6.9 2-min 10°C Cold Water.—During the CPM task (described below), participants were asked to place their right hand in a 2-min circulating cold water bath held at 10°C, after which they rated their cold pain using a computerized NRS (0 “no pain”, 20 “mild pain”, 40 “moderate pain”, 60 “severe pain”, 80 “very severe pain”, and 100 “worst possible pain”). Although its primary use was for CPM, it also serves as a measure of suprathreshold pain sensitivity.

2.7 Measures of Central Sensitization

2.7.1 Nociceptive Flexion Reflex (NFR) Threshold.—NFR is a polysynaptic, spinal reflex elicited in response to Aδ fiber activation, so it is used as a measure of spinal nociception[82]. NFR was measured from left biceps femoris EMG using 2 Ag-AgCl electrodes positioned approximately 10 cm superior to the popliteal fossa. A common reference electrode was placed over the lateral epicondyle of the femur. Sensors were filled with conductive gel (EC60; Grass Technologies). The EMG signal was collected, filtered (10 Hz to 300 Hz), and amplified (×10,000) using a Grass Technologies (West Warwick, RI) Model 15LT amplifier (with AC Module 15A54). The skin was cleaned with alcohol and exfoliated (Nuprep gel; Weaver and Company, Aurora, CO) to achieve impedances <5kΩ. EMG was sampled and digitized at 1000 Hz using a National Instruments analog-to-digital converter (Austin, TX).

NFR threshold (the stimulus intensity necessary to elicit the reflex) was used as a static measure of spinal nociceptive sensitivity (lower thresholds=greater sensitization). NFR threshold was assessed from 3 ascending-descending staircases of stimulations[74]. The first staircase began at 0 mA and increased in 2 mA increments until a reflex was observed (defined as when the averaged, rectified EMG activity of the biceps femoris in the 90 to 150 ms post-stimulus interval was 1.4 SD greater than the averaged, rectified biceps femoris EMG activity during the 60 ms pre-stimulus baseline interval) [74]. Once an NFR was obtained, the stimulus intensity decreased in 1 mA steps until a reflex was not observed. The second and third ascending-descending staircases used 1 mA step increments. The interval between electric stimuli varied randomly (8 to 12 s) to minimize predictability and reflex habituation. NFR threshold was defined as the average stimulus intensity (mA) of the two peaks and two troughs of the last 2 ascending-descending staircases.

In the event that stimulations at NFR threshold were not experienced as painful, the stimulation intensity was increased from NFR threshold in 2 mA steps until a rating of 30 was achieved on the VAS (ie, Pain30; this was only used for stimulation intensity determination for CPM and thus not reported here).

2.7.2 3-Stimulation Threshold.—3-stimulation threshold was defined as the stimulus intensity required to evoke an NFR on the last stimulus of a series of 3 electric stimulations. To assess this, a series of 3 electric stimulations were delivered with an inter-stimulus interval of 0.5 s (2.0 Hz). The series started at 0 mA and increased in 2 mA steps until an NFR was evoked by the third stimulus in the series. The stimulus intensity at which the NFR was evoked was used as 3-stimulation threshold. This task is akin to what has been described in the literature as temporal summation of NFR threshold[54]; however, its definition does not require summation of the reflex across the 3 stimulus series (reflexes could decrease across the 3 stimulations, although this rarely happens based on our experience).

2.7.3 Temporal Summation of NFR (TS-NFR).—TS-NFR assesses the degree of spinal neuron excitability following a series of suprathreshold stimulations[94], and is believed to be a correlate of windup in animals[63;110;111]. The suprathreshold stimulus intensity used for this task was set at 120% of NFR threshold or 120% of 3-stimulation threshold, whichever was higher (in mA). In the present study, TS-NFR was defined as the degree of reflex summation following a series of 3 suprathreshold stimuli. To assess this, 5 trains of 3 suprathreshold stimuli (0.5 s ISI) were used to assess temporal summation. After each train of stimuli, participants were instructed to rate the pain intensity corresponding to each of the 3 stimulations, using a set of 3 computer-presented VASs ranging from “no pain sensation” to “the most intense pain sensation imaginable.” After the participant completed the ratings, there was an inter-train interval of 8-12 s. The baseline EMG in the 60 ms prior to the third stimulus in the stimulus series was visually inspected in real-time by the experimenter for excessive muscle tension or voluntary movement. If the mean rectified EMG exceeded 5 μ V, the train was repeated in order to ensure that EMG activity in the post-stimulus interval was not contaminated by muscle tension unrelated to the NFR[94]. NFR magnitudes in response to each stimulus in the 3-stimulus train were calculated in d-units by first subtracting the 60 ms baseline prior to the first stimulus in each train from the EMG

response 70-150 ms after each stimulus in the train. This difference was then divided by the average of the standard deviations of the rectified EMG from these two intervals. Note: the post-stimulus interval used here differs from the assessment of NFRs in response to single stimuli (ie, 90-150 ms post-stimulus) because repeated stimulations with a short (0.5 s) inter-stimulus interval can result in a shorter NFR onset latency[94].

2.7.4 Temporal Summation of Electric Pain (TS-Electric Pain).—Temporal summation of pain is believed to be the perceptual correlate of windup in animals[90]. For this study, TS-Electric Pain was defined in two ways. First, it was defined as the increase in pain across the 3-stimulus train described in the TS-NFR section above. However, this approach is limited because participants are asked to make ratings of all 3 stimuli after the series has been delivered because there is not enough time to rate stimuli in the 0.5 s inter-stimulus interval. This retrospective reporting could result in bias, particularly because the perception of the first 2 stimuli could be influenced by the more painful third stimulus. To overcome this problem, 5 single electric stimuli were delivered using the same suprathreshold intensity (8-12 s interstimulus interval) and participants made pain ratings using the same VAS immediately after each stimulation. Thus, like Farrell and Gibson[33], TS-Electric Pain was also defined as the difference between ratings of these single stimuli and the rating of the 3rd stimulus in the 3-stimulus train. Both definitions were used in analyses.

2.7.5 Temporal Summation of Heat Pain (TS-Heat Pain).—Temporal summation of heat pain was measured in response to 5 trains of 10 suprathreshold heat stimuli according to published procedures[88;89]. The first train was a practice and the remaining 4 were used in analyses. The stimulus intensity was individually calibrated to each participant (ie, Heat Pain45 described above). Prior to the TS-Heat Pain task, participants were instructed on the difference between first and second pain. During each train, the NRS was continuously displayed and participants were asked to call out a numerical rating after each heat pulse corresponding to their second pain which was recorded by the experimenter. Heat pulses in the series had a start to start inter-stimulus interval of 2.5 s and each pulse started at a 35 °C baseline, reached the peak temp in 0.5 s, held the peak temperature for .5 s, and then returned to baseline in .5 s [88;89]. However, after 24 participants were ran using these parameters, examination of the data suggested almost no one was showing pain summation, so the heat parameters were changed based on the recommendations of Kong et al[46] (baseline temperature changed from 35°C to 39°C, ramp up and ramp down speed changed from 0.5 s to 0.37 s, peak temperature duration changed from .5 s to .75 s; pulse to pulse interval stayed 2.5 s). However, this did not improve pain summation; thus, analysis of TS-Heat Pain ignored the difference in these two parameter variants after demonstrating no significant difference between the two (there were no differences in average pain ratings or summation of pain ratings based on the two stimulus parameters).

2.8 CNS Inhibition: Conditioned Pain Modulation (CPM)

The CPM task was used to assess descending inhibition. In this study, CPM involved the assessment of pain and NFR in response to a test stimuli before, during, and after a tonic conditioning stimulus (CS) delivered at a distal body site from the test stimulus. In healthy

humans, the CS should inhibit pain evoked by the test stimuli[43]. The test stimuli were electrical stimulations (intensity = highest of 120% NFR threshold, 120% temporal summation threshold, or 100% electric Pain30) delivered to the left ankle, as well as 52°C heat pulses delivered to the left volar forearm (heat started at baseline of 32°C increased to 52°C at a rate of 70°C/s and then returned to baseline at a rate of 40°C/s). The CS was exposure to a 2-min long circulating cold-water bath maintained at a temperature of $10\pm0.1^{\circ}\text{C}$.

CPM consisted of three 2-min phases: baseline (test stimuli delivered prior to cold water), conditioning (test stimuli delivered while hand/arm is submerged in cold water), and post-test (test stimuli delivered after conditioning). A 2-min rest occurred between baseline and conditioning and a 5-min rest occurred between conditioning and post-test. During conditioning, participants were instructed to submerge their right hand up to their forearm in the painfully cold water and to keep their hand palm down with fingers spread. Each 2-min phase, consisted of a 20 s wait period, followed by 5 electric test stimuli (random 8-12 s inter-stimulus interval) and then five 52°C heat pulses (random 4-8 s inter-stimulus interval). Participants provided pain ratings in response to the electric stimulations verbally using a NRS that was constantly displayed (0 “no pain”, 20 “mild pain”, 40 “moderate pain”, 60 “severe pain”, 80 “very severe pain”, and 100 “worst possible pain”) and an experimenter recorded the ratings. Pain ratings of heat stimuli were made using the same NRS immediately after the last heat pulse (this was done so that making ratings of heat pulses would not interfere with physiological responses; physiological data not presented). Following the conditioning phase, participants used the NRS to rate the pain evoked by the cold water.

NFR magnitudes in response to electric stimuli were used to assess within-subjects changes in spinal nociception[75]. NFR magnitudes were calculated as a d-score [NFR $d = (\text{mean rectified EMG of 90 to 150 ms post-stimulation interval} - \text{mean of rectified EMG from } -60 \text{ to } 0 \text{ ms prestimulation interval}) / \text{average standard deviation of the rectified EMG from the two intervals}$]. Trials with NFR baselines higher than 3.0 μV were excluded from analyses due to excessive muscle tension and/or noise in the recording (3% of trials were excluded).

A “sham” CPM task was also employed as a control condition. Sham CPM was identical to the real CPM task with the exception that a 26°C non-painful water bath was used. The order of CPM and sham CPM was randomized and there was a 15 min break between the two to avoid carry over effects.

2.9 Data Analysis

2.9.1 Data Screening.—Prior to analyses, variable distributions were screened using boxplots, histograms, and normality statistics. Those that were skewed were log or square transformed to reduce positive and negative skew, respectively. If a variable was transformed, this is noted in the Results section and/or Tables, and the reverse transformed means in original units are depicted in Figures. Next, outliers were identified using Wilcox’s MAD-median procedure (using the recommended 2.24 cutoff) and then winsorized by replacing the outlier value with the next nearest non-outlier value [108]. The following

variables were winsorized as a result of outliers (and the number of observations winsorized): BMI (n=3), systolic BP (n=15), diastolic BP (n=5), heart rate (n=12), mean arterial pressure (n=11), pain catastrophizing (n=10), negative affect (n=4), positive affect (n=4), state anxiety (n=5), perceived stress (n=7), psychological distress (n=19), bodily pain (n=35), general health perception (n=15), cool detection threshold (n=25), warm detection threshold (n=25), heat pain threshold (n=19), heat pain tolerance (n=26), stimulus-response curve for heat ratings (n=428 of 5653 trials; 7.6%), cold pressor pain threshold (n=13), cold pressor pain tolerance (n=18), thumb pressure threshold (n=11), trapezius pressure threshold (n=11), masseter pressure threshold (n=16), ischemia pain threshold (n=18), ischemia pain tolerance (n=8), electric pain threshold (n=26), 52°C heat series (n=21), Pain45 heat used for TS-Heat Pain (n=3), NFR threshold (n=12), 3-stimulation threshold (n=20), TS-NFR (104 trials, 2.8%), CPM of NFR (n=40 of 2412 trials; 1.7%), CPM of electric pain (n=77 of 2482 trials; 3.1%), CPM of heat pain (n=57 of 966 trials; 5.9%). When there were missing observations on control variables (see Table 1) they were replaced by the grand mean prior to analyses of primary outcomes to avoid listwise deletion and loss of participants.

2.9.2 Background Characteristics.—Independent-samples t-tests were used to examine group differences on background variables that might affect pain processing. If a variable was found to differ, this was considered as a potential control variable in primary analyses. Significance level was set to $\alpha < .05$ (2-tailed).

2.9.3 Primary analyses.—Traditional (i.e., GLM) ANCOVA models were used to analyze group differences on primary outcomes that were measured on a single occasion or averaged to a single score (i.e., most pain sensitivity measures). Centered control variables were entered as covariates in these models. By contrast, measures of central sensitization (ie, TS-NFR, TS-pain, TS-heat pain) and pain inhibition (ie, CPM) were analyzed using multilevel models (MLM) that examined change in pain outcomes (ie, repeated measures). Centered control variables were entered as covariates. For these analyses, level 1 units were the repeated measures, whereas level 2 units were participants. In most cases, the repeated measures variance-covariance structure was modeled with an autocorrelation matrix (AR1). Significant interactions were followed up with Fishers LSD mean comparisons. Significance level was set to $\alpha < .05$ (2-tailed).

3.0 Results

3.1 Group Differences on Background Characteristics

Table 1 presents N's, means, standard deviations, and inferential statistics for participant characteristics by group. Groups were not different on age, dispositional pain catastrophizing, negative affect, positive affect, state anxiety, bodily pain, general health, biological sex, education level, or income. However, consistent with known physical and psychological health disparities[6;107;112], NAs had higher BMI, systolic and diastolic BP, mean arterial pressure (MAP), resting HR, perceived stress, psychological distress, and poorer sleep quality. There were also group differences in marital status (NAs less likely to be single, more likely to cohabitate) and employment (NAs more likely to have full time job, less likely to be a student), but these are likely sample-specific.

Given these differences, all primary analyses controlled for BMI, MAP (to control for all cardiovascular differences), sleep quality, perceived stress, and psychological distress. Moreover, given well-established sex differences in pain [1;77], sex was added as a control variable, but its influence will not be discussed in order to keep the focus on racial/ethnic differences.

3.2 Peripheral Fiber Function

Cool and warm thresholds were skewed, so they were squared and log transformed, respectively. As shown in Table 2, there were no significant group differences, suggesting that differences in Aδ and C-fiber function did not contribute to pain risk in NAs.

3.3 Pain Sensitivity

To briefly summarize the pain sensitivity results, the only group differences noted were cold pain threshold and tolerance. NAs had increased pain sensitivity (lower threshold/tolerance) on these measures (Table 2, Figure 3).

3.3.1 Heat Pain Threshold/Tolerance.—19 participants were excluded from these analyses for failing to follow instructions (eg, poor effort, pain tolerance lower than pain threshold). As shown in Table 2 and Figure 3, there were no significant group differences on either variable. Thus, groups did not differ in their heat pain thresholds/tolerances.

3.3.2 Stimulus-Response Curve to Heat.—Log transformed heat ratings (N=257; NA=127, NHW=130) were analyzed using a 11 (Temperature) X 2 (Temperature Block) X 2 (Race) MLM ANCOVA model that covaried the control variables. Although there was a significant Race X Temperature interaction [$F(10, 4705)=2.025, p=.027$], no group differences were found when the simple effects of race were examined (all $ps>.13$), so groups had similar stimulus-response curves to heat (Figure 3). There was also no main effect of race [$F(1, 257)=0.250, p=.618$]. Thus, groups did not differ in their sensitivity to heat pulses ranging between 40° and 50° C.

3.3.3 Heat Pain45.—As Table 2 shows, there was no group difference in the Pain45 stimulus intensity. This means that both groups were exposed to similar stimulus intensities during TS-Heat Pain (see results below).

3.3.4 Cold Pressor Pain Threshold/Tolerance.—Both variables were right skewed, so they were log transformed. 3 participants were excluded for failing to follow instructions. As shown in Table 2 and Figure 2, NAs had lower cold pain thresholds and tolerances, suggesting hyperalgesia.

3.3.5 Pressure Pain Thresholds.—As shown in Table 2 and Figure 2, there were no group differences in pressure pain thresholds at any of the 3 body sites (masseter, trapezius, thumb).

3.3.6 Ischemia Pain Threshold/Tolerance.—1 participant was excluded for failing to follow instructions and both variables were log transformed. As shown in Table 2 and Figure 2, there were no group differences in ischemia pain threshold or tolerance.

3.3.7 Electric Pain Threshold/Tolerance.—As shown in Table 2 and Figure 2, there were no group differences in electric pain threshold or tolerance.

3.3.8 52°C Heat Series.—These data were log transformed and analyzed using a 5 (Stimulus Series) x 2 (Race) MLM ANCOVA covarying the control variables. There was no main effect of Race [$F(1,271) < 1$, $p = .945$] or a Race x Stimulus Series interaction [$F(4,573) = 1.421$, $p = .226$]; thus groups did not differ on this measure. Descriptive statistics for the main effect of race are depicted in Table 2 and Figure 2.

3.3.9 2-min 10°C Cold Water Bath (from CPM).—As shown in Table 2 and Figure 2, there were no group differences in pain ratings in response to the 2-min circulating cold water bath. Further, this means that the painfulness of the conditioning stimulus used during CPM did not differ between groups.

3.4 Central Sensitization

To briefly summarize these findings, groups did not significantly differ on any measure of central sensitization, indicating that pain risk in healthy NAs is not due to differences in central sensitization.

3.4.1 NFR Threshold.—As shown in Table 2 and Figure 2, groups did not differ in NFR threshold, indicating that spinal sensitization was similar between groups.

3.4.2 3-stimulation Threshold.—As shown in Table 2 and Figure 2, groups did not differ in 3-stimulation threshold, indicating that spinal sensitization was similar between groups.

3.4.3 TS-NFR and TS-Electric Pain.—These data were analyzed using a multilevel growth model approach in which the summation slope was modeled using a linear trend (TS Slope). Race, trial number (coding for the 5 different stimulus trains) and the centered control variables were also entered as predictors. Growth model results for TS-NFR and TS-Electric Pain are presented in Table 3 and outcomes are depicted in Figure 4. In brief, both groups showed significant summation of NFR and electric pain (across the 3-stimulus series and single stimulations vs. triple stimulations), but groups did not differ in the degree of summation.

271 participants (135 NHW, 136 NA) participated in these TS tasks. 12 participants (6 NHW, 6 NA) were excluded from TS-NFR analyses because their EMG was contaminated by voluntary movement. Thus, 259 participants contributed data. Results for TS-NFR indicated that both groups showed significant summation of NFR as indicated by the significant TS Slope effect, but groups did not differ in their degree of summation (Table 3, Fig 4).

31 participants (15 NHW, 16 NA) were excluded from analyses of ratings from the 3 stimulus train, because ratings of stimulation 1 were either at ceiling ($VAS \geq 95$) or floor ($VAS \leq 5$). Thus, 240 participants contributed data. The main effect of TS Slope indicated that pain summated, but this summation did not differ between groups (Table 3, Fig 4).

27 participants (12 NHW, 15 NA) were excluded from analysis of TS-Pain defined as the difference between single stimulations and the 3 stimulus train because ratings of the single stimulations were at ceiling ($VAS \geq 95$) or floor ($VAS \leq 5$). Thus, 244 participants contributed data. The main effect of TS Slope indicated that pain summated, but this summation did not differ between groups (Table 3, Fig 4).

3.4.4 TS-Heat Pain.—TS-Heat Pain ratings were analyzed using a 2 (Race) x 10 (TS Slope) x 4 (Trial Number) MLM ANCOVA model that covaried the control variables. 260 participants had TS-Heat Pain data available for analysis (NA=128, NHW=132). There was a significant TS Slope main effect [$F(9, 8083)=328.52, p<.001$] suggesting that pain ratings decreased across the 10 pulse heat series (ie, habituated), but that effect was qualified by a significant Race x TS Slope interaction [$F(9, 8231)=3.24, p=.001$]. Despite this interaction, there were no significant differences between NAs and NHWs on any of the 10 ratings of the heat stimulus series suggesting both groups habituated to the heat pulses at the same rate (Figure 5).

3.5 Conditioned Modulation of Pain and NFR

Two approaches were taken to analyzing CPM of NFR, CPM of electric pain, and CPM of heat pain. One approach examined the difference in pain/NFR between the baseline period and the conditioning period of the active CPM task. To do so, 2 (CPM phase: baseline vs. conditioning) x 2 (Race) MLM ANCOVAs were used that covaried the control variables. The second approach examined the difference in pain/NFR between the cold pressor conditioning phase and the sham (non-painful water) conditioning phase. To do so, 2 (Conditioning Type: Cold vs. Sham) x 2 (Race) MLM ANCOVAs were used that covaried the control variables. Results are presented in Table 4 and Figure 6. In brief, both groups showed significant CPM of electric pain and heat pain, but did not differ from one another. Neither group showed significant CPM of NFR.

256 participants participated in the CPM tasks, but 2 participants were excluded from CPM analyses for not following instructions. Thus, there were 254 considered for analysis (129 NHW, 125 NA).

3.5.1 CPM of NFR.—3 participants (2 NHW, 1 NA) were excluded from CPM of NFR analyses because their EMG was contaminated by voluntary muscle activity and 1 participant's NFR data were lost due to equipment failure. As shown in Table 4 and Figure 6, there were no group differences in CPM of NFR when comparing the baseline period to the conditioning period, or when the sham conditioning period was compared to the conditioning period. Moreover, neither group showed significant inhibition of NFR, although there was a trend for the NHW group to show inhibition when baseline was compared to conditioning ($p=.05$; see Fig 6).

3.5.2 CPM of Electric Pain.—4 participants (3 NA, 1 NHW) were excluded from analyses of CPM of electric pain, because all ratings during baseline were at ceiling ($VAS \geq 95$). None were at a floor ($VAS \leq 5$). Thus, 250 participants contributed data. As shown in Table 4, when the baseline period was compared to the conditioning period there was a significant Race x CPM Phase interaction. This interaction was also found in the analysis that compared conditioning to sham conditioning. However, in both cases, simple effects tests did not find a group difference in the inhibition of pain ($ps > .05$, Figure 6). Thus, both groups showed similar electric pain inhibition (ie, there were no detectable group differences).

3.5.3 CPM of Heat Pain.—9 participants (5 NA, 4 NHW) were excluded from analyses of CPM of heat pain, because all ratings during baseline were at floor ($VAS \leq 5$). None were at ceiling. Thus, 245 participants contributed data. As shown in Table 4 and Figure 6, both groups showed significant inhibition of heat pain in the analysis that compared baseline to conditioning and the analysis that compared conditioning to sham. However, there were no group differences in this inhibition.

4.0 Discussion

Contrary to hypotheses, there were no group differences on measures of peripheral fibers, central sensitization, CNS inhibition, or pain sensitivity, except that NAs had *lower* cold thresholds/tolerances (ie, greater cold pain sensitivity). To understand these results, it is important to consider the results from another recent OK-SNAP paper that examined subjective responses to pain tasks (McGill Short-Form sensory and affect ratings, pain-related anxiety, situational pain catastrophizing). Those analyses showed that, compared to NHWs, NAs reported greater pain-related anxiety and situational catastrophizing during pain[76], which we interpreted to mean that NAs have a stronger affective-motivational reaction to pain. The current difference in cold pain is consistent with this interpretation, because cold pressor evokes a strong affective response[71]. However, it is worth noting that other tasks (eg, ischemia) also evoke notable affective reactions[71]. So when taken together, a stronger affective-motivational reaction to pain (ie, greater pain-related anxiety/situational catastrophizing) might place NAs at higher risk for chronic pain and suffering[53;68;92].

To further examine this possibility, two subsequent papers have used bootstrapped mediation analyses to test whether pain-related anxiety and situational catastrophizing provide indirect pathways linking NAs with pro-nociceptive processes (eg, NA race anxiety reduced CPM). Results indicated pain-related anxiety mediated relationships with lower pain tolerances (electric, cold, ischemic, heat) and ineffective CPM of NFR (Rhudy et al, under review). Further, situational catastrophizing mediated a relationship with ineffective CPM of NFR (Toledo et al, under review)[99]. These data suggest that there are racial/ethnic differences in pain processing that stem from NAs greater affective-motivational reactions to painful input.

It is currently unclear why OK-SNAP results are not consistent with our original pilot study, but there are a few study differences worth considering. First, the pilot study was small, so it is possible the results were impacted by sampling error. Second, there are some notable sample differences. Average ages were lower in OK-SNAP (NHW=28.5, NA=30.8)

compared to the pilot study (NHW=33.6, NA=41.1), particularly for the NA group. Moreover, blood pressure and BMI were slightly lower in OK-SNAP. And finally, because the pilot study had a small sample size, this precluded statistical control of potential confounding variables in the analyses. Given these issues, it will be important to replicate our findings to establish the stability of the conclusions.

4.1 Integration with the Literature, Implications, and Future Directions

Accumulating evidence indicates that race/ethnicity can play a role in pain experience and chronic pain prevalence[15;17;28;30;31;38;41;42;44;45;52;59;61;69;72;79;84;104;109]. To date, the majority of this work has been conducted with African-American and Hispanic populations, but the number of studies examining other racial/ethnic groups is growing. These studies generally find that ethnic/racial groups who are at higher risk for chronic pain have lower pain tolerances and report more pain in response to suprathreshold stimuli[14;44;69]. This is believed to be due, in part, to central sensitization (hyperexcitability of spinal cord neurons). Supporting this, studies have found greater temporal summation of pain in response to heat[24;38;61;78] and mechanical pressure[38;78] in ethnic/racial minorities. Although it is possible that these ethnic/racial differences represent a general bias towards greater pain report within these groups, this cannot account for the fact that Campbell et al found African-Americans had a lower threshold on the physiologically-derived NFR[17], indicating greater spinal neuron sensitization. Thus, there is some physiological evidence that pain signals are amplified in African-Americans.

A dysfunction of CNS pain inhibition may also contribute to racial/ethnic differences in pain because CPM-related inhibition[16;24] and stress-induced analgesia[62] are less effective in African-Americans. Given these findings, one implication of the current study is that the mechanisms of chronic pain in NAs are not the same as those in other racial/ethnic minorities (especially in African-Americans), because NAs do not show enhanced central sensitization or reduced CNS pain inhibition in the absence of anxiety/catastrophizing. When all of the OK-SNAP findings are taken together, they imply that interventions to prevent chronic pain that focus on how to dampen affective-motivational reactions to pain may be helpful for NAs. Indeed, cognitive-behavioral techniques that target anxiety and catastrophizing reactions to improve pain tolerance may be particularly effective[3;83;95]. Given the group difference in cold pain, these treatments could incorporate graded exposure to cold water. Moreover, it has been reported that some NAs are reluctant to engage in conventional treatments[42]; therefore, treatments may need to be tailored to include traditional practices (eg, smudging)[11;42].

The present study focused only on between-group differences in pain processing that might contribute to NA pain risk and there are likely several within-group differences that affect progression to chronic pain. For example, there may be important cultural (eg, acculturation) or geographic (eg, reservation-dwelling) variables to consider. Moreover, NAs are more likely to experience traumatic/adverse life events[5;6;12;47;50;55;67;80], discrimination[2], and metabolic problems, like diabetes[19]. Given that these latter variables are associated with pain risk[29;35;56], then it is possible that they could also contribute to the higher

chronic pain prevalence in NAs. Even if the relationships between these factors and pain are not stronger in (or specific to) NAs (ie, relationships not moderated by race), they could still contribute to NA pain disparities because the base rates of these risk factors are higher in NAs (so they could mediate the relationship between NA race and pro-nociceptive outcomes). Additional OK-SNAP papers will address within-group factors[40;48;91;98].

As noted, we used stringent inclusion criteria to rule out confounding factors and to help ensure that groups were as similar as possible on background variables. Thus, it is possible this strategy excluded NAs at the highest risk for developing chronic pain, impairing our ability to identify between-group mechanisms that promote pain. While possible, it did not appear to eliminate the elevated pain risk in NAs. Every 6-months we contact participants (by phone/mail) to assess for onset of chronic pain (pain lasting >3-months, that does not remit at future assessments). 73% have responded to our follow-up screens and 16% of those have developed chronic pain. Preliminary analyses of these follow-up data suggest NAs are developing chronic pain at 3x the rate of NHWs[81]. So, even though NAs were healthy and pain-free when they enrolled in OK-SNAP, they are developing pain at a higher rate. Once follow-up data collection is complete, it will be important to determine whether individual differences in pain processing that were measured in the present study can help explain what promotes chronic pain in NAs.

4.2 Strengths and Limitations

OK-SNAP is the largest, most comprehensive study of NA pain processing, and is one of the largest studies of racial/ethnic differences in pain mechanisms to date[44]. It also used numerous pain stimulus modalities, assessed subjective and physiological outcomes, and addressed multiple aspects of the pain system (peripheral, spinal, inhibitory, perceptual). Tasks and testing days were pseudorandomly ordered or counterbalanced to minimize order effects. Potential confounds were either experimentally or statistically controlled. Moreover, most testing was administered by computer and experimenters observed from an adjacent room to minimize bias and/or experimenter effects on participant responses. Despite these strengths, a few limitations should be mentioned.

As noted, only healthy, pain-free individuals were recruited to determine whether pre-existing differences in pain processing are present that contribute to chronic pain risk in NAs. Although this helps ensure that observed group differences are not due to disease status and/or access to health care, we do not know whether our findings will generalize to NAs with chronic pain or to older adults (given that the sample was relatively young). Second, even though we varied the order of tasks and scheduled mandatory breaks, it is possible that some carryover occurred that might have obscured some racial/ethnic differences. Third, our NA participants were recruited mostly from northeastern Oklahoma where the majority of NAs are not reservation-dwelling. It is not clear if our results will generalize to NAs from other geographical regions, particularly those living on reservations where access to health care may be more limited. Fourth, although we chose tasks intended to comprehensively assess the pain system, there may be other tasks more sensitive to racial/ethnic differences in pain processing (eg, topical capsaicin)[37;104]. Fifth, because this was one of the first studies to examine pain risk mechanisms in NAs we did not adjust for

familywise type I error rate in order to ensure that potentially important differences were not missed. However, this may explain why only two significant differences (cold pain) were found among the large number of comparisons. And finally, this study was cross-sectional so we cannot guarantee that responses to pain tasks were stable estimates of each participant's pain processing and not influenced by recent events in their lives.

4.3 Summary

This study found that there were no differences between NAs and NHWs on measures of peripheral fiber function, spinal (central) sensitization, CNS pain inhibition, and most measures of pain threshold/tolerance. Surprisingly, the only difference was that NAs had lower cold pain thresholds/tolerances than NHWs, indicating they were more pain sensitive. Together, this suggests that pain risk in NAs may be different than other U.S. minority groups who show greater CNS excitability, reduced pain inhibition, and generally enhanced pain sensitivity. Future studies are needed to identify other factors that contribute to their pain risk.

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Figure 1.

Study procedures. Testing was conducted over a two day period (approximately 1 week apart) with testing day order counterbalanced. Most pain sensitivity tests were conducted on one day, whereas most pain modulation tasks were conducted on another day.

Figure 2.

Group differences on thermal detection thresholds (cool detection threshold [CDT], warm detection thresholds [WDT]), pain sensitivity measures (heat pain threshold [Hthr], heat pain tolerance [Htol], cold pain threshold [Cthr], cold pain tolerance [Ctol], pressure pain thresholds measured at masseter, trapezius, and thumb, ischemia pain threshold [IschThr], ischemia pain tolerance [IschTol], electric pain threshold [Ethr], electric pain tolerance [Etol]), suprathreshold pain measures (52°C heat pulses [52°C heat], 2-min 10°C circulating water [10°C cold], and two measures of central sensitization (nociceptive flexion reflex threshold [NFRthr], 3-stimulation threshold [3-StimThr]). Variables that were transformed were reverse transformed for the figure; therefore, no error bars are displayed (see Table 2). * $p < .05$

Figure 3.

Group differences in the stimulus-response curve to heat stimuli. Native Americans (NAs) and non-Hispanic whites (NHWs) displayed similar ratings of heat pulses ranging from 40 to 50 °C. NRS=numerical rating scale. Means were reversed transformed.

Figure 4. Group differences in temporal summation of the nociceptive flexion reflex (TS-NFR) and electric pain (TS-Pain). Native Americans (NA) and non-Hispanic whites (NHW) displayed similar TS-NFR and TS-Pain.

Figure 5.

Group differences in response to a 10 pulse heat series intended to evoke temporal summation of heat pain (TS-Heat Pain). Native Americans (NA) and non-Hispanic whites (NHW) both displayed similar habituation (not summation) in response to the 10 stimulus heat series.

Figure 6. Group differences in conditioned pain modulation (CPM) of the nociceptive flexion reflex (NFR), electric pain, and heat pain. Graphs on the left depict comparisons between baseline and conditioning phases of CPM, whereas graphs on the right depict comparisons between sham conditioning and conditioning. There was no effect of race/ethnicity on CPM of NFR, but the only evidence for inhibition of NFR was found by a marginal simple effect of CPM phase (top left graph). Although there was a significant Race x CPM Phase effect for electric pain, there were no group differences when simple effects were examined. Thus, together these results indicate that Native Americans (NA) and non-Hispanic whites (NHW) showed similar CPM-related inhibition of pain. * $p < .05$

Table 1.

Participant characteristics by racial/ethnic group

Continuous Variables	NHW (N=150)			NA (N=155)			Cohen's d	t	df	p-value
	N	M	SD	N	M	SD				
Age (years)	150	28.500	13.505	155	30.819	12.785	-0.176	-1.541	303	0.124
BMI (kg/m ²)	149	24.130	3.730	151	25.984	4.516	-0.448	-3.881	289.057	<0.001
Systolic BP (mmHg)	148	113.971	9.939	149	119.609	12.783	-0.492	-4.245	278.94	<0.001
Diastolic BP (mmHg)	148	68.712	7.836	149	74.081	9.649	-0.611	-5.265	283.813	<0.001
Mean Arterial Pressure (mmHg)	148	82.820	7.226	149	88.313	9.704	-0.642	-5.536	273.535	<0.001
Resting HR (bpm)	148	64.367	10.245	149	66.906	10.463	-0.245	-2.113	295	0.035
Dispositional Pain Catastrophizing (PCS; 0-52)	149	9.403	7.443	152	9.776	7.781	-0.049	-0.426	299	0.671
Negative Affect (PANAS; 10-50)	149	2.799	2.617	152	3.059	2.579	-0.100	-0.870	299	0.385
Positive Affect (PANAS; 10-50)	135	18.119	6.917	134	19.000	7.738	-0.120	-0.985	267	0.325
State Anxiety (STAI; 20-80)	149	32.074	7.047	152	33.105	7.193	-0.145	-1.256	299	0.210
Poor Sleep Quality (PSQI; 0-3)	118	0.958	0.632	116	1.259	0.846	-0.404	-3.079	212.938	0.002
Perceived Stress (PSS; 0-40)	147	13.000	5.866	148	14.460	6.090	-0.244	-2.096	293	0.037
Psychological Distress (SCL-90 log GSI)	147	0.105	0.076	148	0.135	0.095	-0.349	-3.004	280.644	0.003
Bodily Pain (SF-36; 0-100)	135	43.526	6.729	135	42.830	7.691	0.096	0.792	268	0.429
General Health Scale (SF-36; 0-100)	147	65.318	9.412	149	62.949	11.409	0.226	1.950	285.094	0.052
Categorical Variables										
Female Sex	74		49.3%	91		58.7%		Chi Square	df	p-value
Marital Status										
single	112		74.7%	94		61.8%				
married	24		16.0%	32		21.1%				
separated/divorced/widowed	12		8.0%	15		9.9%				
cohabitating	2		1.3%	11		7.2%				
Education Level										
<HS	3		2.0%	8		5.2%		3.933	4	0.415

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Employment	HS grad	21	14.1%	26	16.9%	11.393	4	0.022
	partial college	76	51.0%	65	42.2%			
	college grad	38	25.5%	43	27.9%			
	Grad/Prof training	11	7.4%	12	7.8%			
Non-employed student	40 hrs/wk	32	21.8%	49	32.0%	8.247	7	0.311
	<40 hrs/wk	67	45.6%	54	35.3%			
	retired	5	3.4%	3	2.0%			
	unemployed	27	18.4%	40	26.1%			
	Non-employed student	16	10.9%	7	4.6%			
Income	<\$10K	57	38.8%	40	26.7%	8.247	7	0.311
	\$10K-\$15K	18	12.2%	18	12.0%			
	\$15K-\$25K	17	11.6%	20	13.3%			
	\$25K-\$35K	11	7.5%	16	10.7%			
	\$35K-\$50K	14	9.5%	25	16.7%			
	\$50K-\$75K	8	5.4%	12	8.0%			
	\$75K-\$100K	9	6.1%	8	5.3%			
	>\$100K	13	8.8%	11	7.3%			

Note: Bolded variables were significant at $P < .05$. t -tests with non-integer degrees of freedom (df) were corrected for heterogeneous variances. BMI = body mass index. BP = blood pressure. HR = heart rate. PCS = Pain Catastrophizing Scale. PANAS = Positive and Negative Affect Schedule. STAI = State Trait Anxiety Inventory. PSQI = Pittsburgh Sleep Quality Index. PSS = Perceived Stress Scale. SCL-90 = Symptom Checklist. SF-36 = Medical Outcomes Study Short Form Health Survey.

Table 2.

Means, Standard Deviations, and Inferential Statistics for Native Americans (NA) and non-Hispanic Whites (NHW) on Measures of Peripheral Fiber Function, Pain Sensitivity, and Central Sensitization

Variables	NHW			NA			Inferential Statistics		
	M	SD	N	M	SD	N	F	p	η^2
Peripheral Fiber Function									
Cool Detection Threshold (°C squared)	752.377	76.190	132	743.343	75.086	126	0.190	0.663	0.001
Warm Detection Threshold (log[°C])	1.521	0.014	132	1.526	0.017	127	1.332	0.250	0.005
Pain Sensitivity									
Heat Pain Threshold (°C)	42.189	2.523	126	42.836	2.469	111	1.534	0.217	0.007
Heat Pain Tolerance (°C)	45.900	2.081	125	45.724	1.543	111	1.735	0.189	0.008
Heat Pain45 for TS-Heat Pain (°C)	47.362	1.783	130	47.307	1.858	127	0.726	0.395	0.003
Cold Pressor Pain Threshold (log[sec+1])	1.282	0.235	132	1.233	0.220	126	6.006	0.015	0.023
Cold Pressor Pain Tolerance (log[sec+1])	1.797	0.420	132	1.650	0.310	126	9.240	0.003	0.036
Pressure Pain Threshold (masseter; kPa)	163.306	65.157	132	160.203	61.016	127	0.537	0.464	0.002
Pressure Pain Threshold (trapezius; kPa)	333.899	150.240	131	331.102	155.674	127	0.380	0.538	0.002
Pressure Pain Threshold (thumb; kPa)	493.142	233.347	132	497.885	230.418	127	0.276	0.600	0.001
Ischemia Pain Threshold (log[sec+1])	1.568	0.323	130	1.548	0.387	125	0.404	0.525	0.002
Ischemia Pain Tolerance (log[sec+1])	2.204	0.421	130	2.121	0.449	125	1.665	0.198	0.007
Electric Pain Threshold (0-50 mA)	11.292	6.235	130	11.403	6.110	124	0.101	0.751	<0.001
Electric Pain Tolerance (0-50 mA)	30.600	13.296	130	30.920	13.081	126	0.090	0.765	<0.001
52°C Heat Series (log[VAS+1])	1.072	0.453	134	1.076	0.472	129	0.005	0.945	<0.001
2-min 10°C Cold Water Bath (NRS; 0-100)	51.820	24.266	129	55.910	24.281	122	0.708	0.401	0.003
Central Sensitization									
NFR Threshold (0-50 mA)	16.802	9.977	136	19.488	10.049	142	2.426	0.121	0.009
3-stimulation Threshold (0-50 mA)	13.541	5.641	135	14.865	5.643	141	3.270	0.072	0.012

Note: These means and SDs have been adjusted using the following centered covariates: biological sex, body mass index, mean arterial pressure, sleep quality, perceived stress, and psychological distress. NRS=numerical rating scale. P-values in bold reflect significant group differences at $p < .05$.

Table 3.

Multilevel growth curve model results for group differences in temporal summation of the nociceptive flexion reflex (TS-NFR) and temporal summation of electric pain (TS-Electric Pain)

Dependent Variable	Predictor	Estimate	SE	df	t-value	p-value	95% CI	
							Lower	Upper
TS-NFR	Race	-0.046	0.055	263.855	-0.841	0.401	-0.155	0.062
	TS Slope	0.249	0.023	251.807	10.872	<0.001	0.204	0.295
TS-Pain (3 stims)	Race x TS Slope	0.044	0.032	253.655	1.355	0.177	-0.020	0.108
	Race	1.276	3.436	242.343	0.371	0.711	-5.492	8.044
	TS Slope	1.652	0.322	260.954	5.128	<0.001	1.018	2.287
	Race x TS Slope	0.117	0.445	239.81	0.262	0.794	-0.760	0.993
TS-Pain (single vs. triple)	Race	1.031	3.106	245.685	0.332	0.740	-5.087	7.149
	TS Slope	2.829	0.330	243.923	8.582	<0.001	2.179	3.478
	Race x TS Slope	0.538	0.468	244.079	1.150	0.251	-0.384	1.461

Note: TS Slope codes for the slope of summation across the 3-stimulus series (or the difference between single stims vs. triple stim ratings). All models controlled for trial number, biological sex, body mass index, mean arterial pressure, sleep quality, perceived stress, and psychological distress. The models for TS-pain also controlled for suprathreshold electric stimulus intensity given that it was individually calibrated to each participant based on their NFR threshold (rather than their pain perception). Significant p-values are bolded.

Table 4.

Results of multilevel ANCOVA models for conditioned pain modulation (CPM) of the nociceptive flexion reflex (NFR), electric pain, and heat pain.

Dependent Variable	Independent Variable	df _{num}	df _{denom}	F	p
CPM of NFR (base vs. cond)	CPM Phase	1	686.15	0.86	0.354
	Race	1	249.96	0.406	0.525
	Race x CPM Phase	1	758.656	3.247	0.072
CPM of NFR (sham vs. cold)	Conditioning (Cond) Type	1	742.651	1.005	0.316
	Race	1	250.605	0.725	0.395
	Race x Cond Type	1	782.034	0.487	0.486
CPM of Electric Pain (base vs. cond)	CPM Phase	1	470.585	227.536	<0.001
	Race	1	249.924	0.081	0.776
	Race x CPM Phase	1	1100.569	5.139	0.024
CPM of Electric Pain (sham vs. cold)	Conditioning (Cond) Type	1	487.246	129.794	<0.001
	Race	1	248.7	0.186	0.667
	Race x Cond Type	1	1219.683	13.981	<0.001
CPM of Heat Pain (base vs. cond)	CPM Phase	1	242	58.359	<0.001
	Race	1	242	3.393	0.067
	Race x CPM Phase	1	242	1.19	0.277
CPM of Heat Pain (sham vs. cold)	Conditioning (Cond) Type	1	241.399	26.677	<0.001
	Race	1	242.292	3.668	0.057
	Race x Cond Type	1	241.399	1.652	0.200

Note. Analyses examined two comparisons for each dependent variable (baseline vs. conditioning phase of active CPM; sham conditioning vs. cold pain conditioning). All models controlled for biological sex, body mass index, mean arterial pressure, sleep quality, perceived stress, and psychological distress. The models for CPM of electric pain also controlled for suprathreshold electric stimulus intensity given that it was individually calibrated to each participant based on their NFR threshold (rather than their pain perception). Although there was a significant Race x CPM Phase and Race x Cond Type interaction for electric pain models, the simple effects tests that examined mean comparisons did not find that Native Americans and non-Hispanic whites differed in pain inhibition. Bolded p-values are significant at $p < .05$.