Pain-related anxiety promotes pronociceptive processes in Native Americans: bootstrapped mediation analyses from the Oklahoma Study of Native American Pain Risk

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Abstract
Introduction: Evidence suggests Native Americans (NAs) experience higher rates of chronic pain than the general US population, but the mechanisms contributing to this disparity are poorly understood. Recently, we conducted a study of healthy, pain-free NAs (n = 155), and non-Hispanic whites (NHWs, n = 150) to address this issue and found little evidence that NAs and NHWs differ in pain processing (assessed from multiple quantitative sensory tests). However, NAs reported higher levels of pain-related anxiety during many of the tasks.

Objective: The current study is a secondary analysis of those data to examine whether pain-related anxiety could promote pronociceptive processes in NAs to put them at chronic pain risk.

Methods: Bootstrapped indirect effect tests were conducted to examine whether pain-related anxiety mediated the relationships between race (NHW vs NA) and measures of pain tolerance (electric, heat, ischemia, and cold pressor), temporal summation of pain and the nociceptive flexion reflex (NFR), and conditioned pain modulation of pain/NFR.

Results: Pain-related anxiety mediated the relationships between NA race and pain tolerance and conditioned pain modulation of NFR. Exploratory analyses failed to show that race moderated relationships between pain-related anxiety and pain outcomes.

Conclusion: These findings imply that pain-related anxiety is not a unique mechanism of pain risk for NAs, but that the greater tendency to experience pain-related anxiety by NAs impairs their ability to engage descending inhibition of spinal nociception and decreases their pain tolerance (more so than NHWs). Thus, pain-related anxiety may promote pronociceptive processes in NAs to place them at risk for future chronic pain.

Keywords: Quantitative sensory testing, Ethnic differences, Native Americans, Pain modulation, Pain-related affect, Mediation

1. Introduction

Chronic pain rates are higher in Native Americans (NAs) than the general US population. These conditions include arthritis, back pain, headaches, and dental pain, among others. Despite this, there have been few attempts to understand the mechanisms contributing to this pain disparity.

Recently, our laboratory conducted the Oklahoma Study of Native American Pain Risk (OK-SNAP) to address this issue. A number of quantitative sensory tests (QST) were used to assess peripheral fiber function, spinal cord pain amplification processes (ie, temporal summation [TS]), endogenous pain inhibition (ie, conditioned pain modulation [CPM]), and pain sensitivity (threshold/tolerance) in healthy, pain-free NAs, and non-Hispanic whites (NHWs). To our surprise, results indicated that NAs and NHWs did not differ on any of these measures of pain processing, with the exception that NAs were more sensitive to cold pain. Despite the lack of group differences in QST measures, a robust finding was that NAs reported greater pain-related anxiety in response to painful QST tasks. This is consistent with other evidence that minorities tend to report greater pain-related negative affect in response to clinical pain. Given that negative affect can enhance pain and promote pain-related suffering, greater pain-related
anxiety may create a vicious cycle for NAs that enhances and/or initiates chronic pain (eg, pain → anxiety → pain).15,36,72,74 Indeed, pain-related anxiety may serve as a mechanism that promotes pronociceptive processes (ie, increased pain amplification and decreased pain inhibition) to increase chronic pain risk in NAs. Modern statistical methods (ie, bootstrapped indirect tests) provide a statistically powerful way for researchers to test whether mediated (indirect) pathways exist between 2 variables, even when there is not an observed association between those variables.54,55 Specifically, there may be an indirect relationship between NA race and pain processing outcomes that is mediated by pain-related anxiety (NA → pain-related anxiety → pronociception), even when NA race is not directly related to pain outcomes to generate observable group differences in pain processing (ie, even if there is no "total effect"). If there is an indirect effect in the absence of a total effect, this implies that ethnic/racial differences in pronociceptive processes exist only in the presence of pain-related anxiety.

The current study used bootstrapped analyses to examine the indirect relationships between race (NHW vs NA), pain-related anxiety, and QST tasks that assess pain processing. We examined relationships with endogenous inhibition (CPM) of pain and the nociceptive flexion reflex (NFR; a measure of spinal nociception), TS of pain and TS-NFR, and pain tolerance (assessed from electric, heat, ischemic, and cold stimuli) because these pain outcomes have the greatest potential relationship with chronic pain risk.20,21,86,87 Analyses controlled for possible confounding variables, as well as state anxiety unrelated to pain to isolate the effects of pain-related anxiety. We hypothesized that greater pain-related anxiety experienced by NAs would promote pronociceptive processes thus reducing endogenous inhibition, amplifying TS, and lowering pain tolerance.

Methods

2.1. Participants

Power analyses for the primary aims of the parent (OK-SNAP) study were conducted with G*Power (version 3.1.9.2) and indicated that 120 per group (N = 240 total) would result in power of 0.80 for most QST outcomes. A sensitivity analysis was conducted using this sample size, power = 0.80, and alpha = 0.05 to determine the effect size that could be detected for analyses in these secondary analyses of OK-SNAP data. According to Fritz and MacKinnon,31 240 participants should provide power to detect a standardized, bootstrapped, indirect effect of αβ ≥ 0.10, which seems acceptable.

Healthy, pain-free participants were recruited in OK-SNAP to help ensure that any observed differences in pain processing were not due to disparities in pain condition/etiology, disease severity, and/or pain treatment.11,47,77 Recruitment efforts included tribal and nontribal newspaper ads, fliers, personal communications with NA groups, email announcements, online platforms (eg, Facebook), and word of mouth. Those who appeared eligible after a phone screen were invited to attend a laboratory testing day, which began with a thorough screening for inclusion/exclusion criteria. Data collection occurred between March 2014 and October 2018.

Participants were excluded for (1) <18 years old, (2) history of self-reported cardiovascular, neuroendocrine, musculoskeletal, neurological disorders, (3) chronic pain or current acute pain, (4) body mass index (BMI) ≥ 35 (due to difficulties recording electromyogram for NFR), (5) current/recent use of antidepressants, anxiolytic, analgesic, stimulant, or antihypertensive medication, (6) current psychotic symptoms (assessed by Psychosis Screening Questionnaire) or substance use problems, and/or (7) an inability to read and speak English. Native American status was verified from Certificate of Degree of Indian Blood or tribal membership cards. Native American participants represented tribal nations predominately from the southern plains and eastern Oklahoma tribes. All participants were given an overview of procedures and told they could withdraw at any time before they provided verbal and written informed consent. Participants received a $100 honorarium for the completion of each testing day. The study was approved by IRBs of the University of Tulsa, Cherokee Nation, and the Indian Health Service Oklahoma City Area Office.

Of the 329 found eligible, 247 completed both testing days, 41 completed 1 day, and 39 completed part of 1 day. Two participants’ data were lost due to a computer malfunction. Twenty-two participants were non-NA minorities and thus were excluded from analyses. Thus, 155 NA (64 men) and 150 NHW (76 men) were included in the current study (Table 1).

2.2. Brief overview of procedures

A full description of the parent study is reported elsewhere.62 Testing was conducted over a 2-day period, each lasting 4 to 6 hours. Informed consent and inclusion/exclusion screening were conducted on day 1. On one of the testing days, electric pain tolerance, heat pain tolerance, cold pressor pain tolerance, and ischemia pain tolerance were assessed. Conditioned pain modulation and TS of pain/NFR were assessed on the other testing day. Order of testing day was randomized but blocked by race and sex. Moreover, tests within each day were partly randomized to avoid order effects. Breaks were provided between tasks to minimize carryover.

2.3. Background and control variables

Weight and height were assessed from a medical scale to calculate BMI. Blood pressure (mean arterial blood pressure) was assessed 3 times (3-minute intertest interval) at the beginning of each testing day (Dinamap; GE/Critikon Corporation, Tampa, FL) while participants sat comfortably in a recliner. Other background questionnaires were used to assess dispositional pain catastrophizing (Pain Catastrophizing Scale),75 positive and negative affect before testing (Positive and Negative Affect Schedule),62 state anxiety not specific to pain (State Trait Anxiety Inventory [STAI]),73 perceived sleep quality subscale (Pittsburgh Sleep Quality Index),6 perceived stress (Perceived Stress Scale),12 psychological distress (Global Severity Index of the Symptom Checklist-90-Revised, SCL-90-R),17 general health perception (subscale of the Medical Outcomes Study 36-item Short Form Health Survey [SF-36]),81 and bodily pain (subscale of the SF-36).

2.4. Testing environment and apparatus

Participants were seated in a comfortable reclining chair (Perfect Chair Zero Gravity Recliner, Human Touch, Long Beach, CA) in a sound attenuated and electrically shielded testing room that was adjacent to the room where the experimenter monitored testing. Questionnaires were presented by a computer. Custom-built software (LabVIEW; National Instruments, Austin, TX) was used for experimental control. Electric stimuli were delivered through constant current stimulator (Digitimer DS7A;
Hertfordshire, England) and a bipolar electrode (Nicolet; 30-mm interelectrode distance) filled with a conductive gel (EC60; Grass Technologies, West Warwick, RI) attached over the left ankle.

Nociceptive flexion reflex was measured from left biceps femoris electromyography (EMG) using sensors filled with conductive gel (EC60; Grass Technologies). The signal was collected, filtered (10–300 Hz), and amplified (>10,000) using a Grass Technologies (West Warwick, RI) Model 15LT amplifier (with AC Module 15A54). Electromyography was sampled and digitized at 1000 Hz.

Heat stimuli were delivered using a Medoc (Haifa, Israel) Pathway device with a Contact Heat Evoked Potential Stimulator thermode. A circulating water bath (Thermo Fisher Scientific, Pittsburgh, PA) was used to assess cold tolerance and was also used as the painful conditioning stimulus (CS) in the CPM task. The water level was kept constant (6” deep) across all participants.

### 2.5. 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 until the participant rated the stimulus as the maximum tolerable pain. After each stimulus, the participant rated their pain on a computer-presented visual analog scale (VAS) ranging from “no pain” to “maximum tolerable pain.”

Heat pain tolerance was assessed 5 times (1 practice and 4 averaged trials) by attaching the Contact Heat Evoked Potential Stimulator thermode to the participants’ left volar forearm. 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 intolerable. The maximum intensity for heat tolerance was set to 51°C.

Cold pressor tolerance was assessed by asking participants to submerge their hand and forearm into 6 ± 0.1°C circulating water. During submersion, participants made continuous ratings on the same VAS used during electric tolerance. The time until a rating of maximum tolerable was defined as pain tolerance (or 5 minutes max was reached).

Ischemia tolerance was assessed using a forearm tourniquet test. Participants conducted hand exercises (Lafayette Hand Dynamometer; Lafayette Instrument Company, Lafayette, IN) at 50% grip strength for 2 minutes (1x/s), then raised their arm for 15 seconds to allow for desanguination. A blood pressure cuff was then inflated to 220 mm Hg to occlude blood flow. During occlusion, participants continuously rated their pain on the previously described VAS, and the time taken to achieve a rating of maximum tolerable was defined as pain tolerance (or 25 minutes max was achieved).

### 2.6. Temporal summation and conditioned pain modulation

#### 2.6.1. Determination of electric stimulus intensity for temporal summation and conditioned pain modulation

To determine the electric stimulus intensity (in mA) to use during these tasks, 3 procedures were conducted, as described elsewhere: NFR threshold (3 ascending/descending staircases of electric stimuli used to determine the minimum stimulus intensity needed to evoke NFR), Pain30 (if NFR threshold did not evoke a 30 out of 100 VAS rating, an ascending series of electric stimulations was used to determine stimulus needed to evoke Pain30), and 3-stimulation threshold (ascending staircase of trains of 3 stimuli at 2 Hz that was used to determine the stimulus intensity needed to evoke NFR on the third stimulus in the train). Stimuli during TS-NFR assessment were set at 1.2x NFR threshold or 1.2x of 3-stimulation threshold (whichever was higher), whereas stimuli during CPM assessment were set at the highest of 1.2x NFR threshold, 1.2x 3-stimulation threshold, or 1x Pain30.

#### 2.6.2. Temporal summation-nociceptive flexion reflex

Temporal summation-NFR was defined as the degree of reflex summation after a series of 3 suprathreshold stimuli. To assess this,
5 series of 3 suprathreshold stimuli (0.5-second ISI) were used. After each series, participants were instructed to rate the pain intensity for 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 interseries interval of 8 to 12 seconds. The baseline EMG in the 60 ms before the third stimulus in the stimulus series was visually inspected for excessive muscle tension or voluntary movement (ie, EMG > 5 μV). If present, the series was repeated. Nociceptive flexion reflex magnitudes were calculated in d-units by subtracting the 60-ms baseline before the first stimulus in each series from the EMG response 70 to 150 ms after each stimulus in the train. This difference was then divided by the average of the SDs of the rectified EMG from these 2 intervals. Temporal summation-NFR was defined as the difference in the NFR magnitude in response to the third stimulus in the series minus the NFR magnitude in response to the first stimulus.

### 2.6.3. Temporal summation-Pain

Temporal summation-Pain was defined similar to Farrell and Gibson. Five single electric stimuli were delivered using the same suprathreshold intensity as that used during TS-NFR (8- to 12-second interstimulus interval), and participants made pain ratings using the same VAS immediately after each stimulation. Temporal summation-Pain was defined as the difference between average rating of these single stimuli and the average rating of the third stimulus in the 3-stimulus train delivered during TS-NFR.

### 2.6.4. Conditioned pain modulation

Conditioned pain modulation involved the assessment of pain and NFR in response to electric test stimuli delivered to the ankle before and during a tonic (CS; circulating, 2 minutes, 10 ± 0.1°C water bath). Each CPM phase was 2 minutes and consisted of a 20-second wait period, followed by 5 electric test stimuli (random 8- to 12-second interstimulus interval). There was a 2-minute break between CPM phases. Participants provided electric pain ratings verbally using an NRS that was displayed on a computer screen in front of them (0 “no pain,” 20 “mild pain,” 40 “moderate pain,” 60 “severe pain,” 80 “very severe pain,” and 100 “worst possible pain”). An experimenter recorded the ratings. Nociceptive flexion reflex magnitudes in response to electric test stimuli were used to assess changes in spinal nociception. Nociceptive flexion reflex magnitudes were calculated as a d-score (NFR d = [mean rectified EMG of 90- to 150-ms poststimulation interval minus mean of rectified EMG from 60- to 0-ms prestimulation interval] divided by the average SD of the rectified EMG from the 2 intervals). Trials with NFR baselines higher than 3.0 μV were excluded (3% of trials were excluded). Conditioned pain modulation of pain/NFR was defined as the difference in the average electric pain/NFR during the CS minus the average electric pain/NFR during the baseline phase.

### 2.7. Pain-related anxiety

Pain-related anxiety was measured from a VAS with the anchors “not at all anxious” and “extremely anxious.” The computer converted the participant’s response to scores that ranged from 0 to 100. The VAS was presented following the pain tasks with the instructions: “Using this scale, rate how anxious you feel.” Although different stimuli evoked different mean levels of pain-related anxiety, the 10 items loaded onto a single component in a principal component analysis, and Cronbach’s alpha was high (α = 0.91). Thus, the items were averaged to create a global pain-related anxiety score. The correlation between pain-related anxiety and state anxiety (from STAI) was r = 0.219; therefore, the degree of overlap with non–pain-related anxiety was minimal.

### 2.8. Data analysis

Cold pressor tolerance, ischemia tolerance, and psychological distress (Global Severity Index) were transformed to reduce positive skew. Outliers were identified using established procedures and then winsorized to the next nearest nonoutlier value. Missing observations on control variables were replaced by the grand mean to avoid listwise deletion. A few participants were excluded from analyses for failing to follow instructions (eg, poor effort, pain tolerance lower than pain threshold) for a full description see Ref. 62.

Independent-samples t-tests or χ² analyses were used to examine group differences on background variables. If group differences were found, this was considered as a potential control...
variable in primary analyses. PROCESS software (v3.3) was used to conduct bootstrapped mediation analyses from 5000 random samples.50 Significant mediation occurs when 0 is not contained in the 95% bootstrapped confidence interval for the indirect effect. Analyses of CPM of pain and TS-Pain controlled for electric stimulus intensity. Moreover, all analyses controlled for STAI state anxiety before the interaction. None of the race × pain-related anxiety interactions were significant (Table 3), indicating that relationships between pain-related anxiety and pain outcomes did not differ between NHWs and NAs.

3.3. Exploratory moderation analyses
To examine whether race moderates the relationships between pain-related anxiety and pain outcomes, we conducted bootstrapped hierarchical regression analyses in PROCESS and entered control variables and the main effects of race and pain-related anxiety before the interaction. None of the race × pain-related anxiety interactions were significant (Table 3), indicating that relationships between pain-related anxiety and pain outcomes did not differ between NHWs and NAs.

4. Discussion
We have previously shown that NAs and NHWs are similar in peripheral nociceptive fiber function, spinal amplification, endogenous pain inhibition, and pain sensitivity (except cold pain).52 By contrast, NAs experienced more pain-related anxiety than NHWs.51 Interestingly, NAs do not report more anxiety unrelated to pain (ie, STAI). Given this, the current study tested whether pain-related anxiety might promote pronociceptive processes in NAs. We found that pain-related anxiety mediated the relationship between NA race and pain tolerance measures, as well as CPM-related inhibition of the NFR. It did not mediate relationships with CPM of pain, or TS (TS-Pain and TS-NFR).

4.1. Implications
These findings have several implications. First, they suggest that stronger affective-motivational reactions play a role in pain risk for NAs. There is a large existing literature suggesting that negative affect (especially pain-related anxiety) can facilitate experimental and clinical pain.15,23,36,52,64,70,72,74 Our results support this and underscore the importance of this relationship for NAs because pain-related anxiety served as a mechanism linking NAs to pronociceptive processes. We believe this may also contribute to their increased chronic pain risk (Fig. 3).

Second, pain-related anxiety may promote pain risk in NAs, not because it is a unique mechanism, but because NAs experience greater pain-related anxiety. Exploratory moderation analyses found that race and pain-related anxiety did not interact to predict any pain outcome. This demonstrates that the strength of the relationships between pain-related anxiety and pain outcomes does not vary between NAs and NHWs. Instead, greater pain-related anxiety experienced by NAs pushes them farther along a pain risk continuum because pain-related anxiety is a pronociceptive process.

Third, pain-related anxiety disrupts descending inhibition of spinal nociception (NFR) in NAs without impairing endogenous inhibition of pain and without promoting spinal sensitization (temporary hyperexcitability of dorsal horn neurons due to peripheral input, as assessed by TS-NFR).25,85 Figure 2 shows that pain-related anxiety may even tip the modulatory balance of NFR (Fig. 1). Thus, pain-related anxiety provides a mechanism linking NA status with lower tolerances and reduced ability to inhibit NFR. Notably, STAI state anxiety was nonsignificant in all models (data not shown). To help visualize these effects, Figure 2 depicts predicted values on dependent variables at group-specific 25th and 75th percentiles for pain-related anxiety (NA: 25th% = 25.50, 75th% = 58.58; NHW: 25th% = 18.70, 75th% = 51.50). As shown, pain-related anxiety generally resulted in lower pain tolerances and reduced NFR inhibition during CPM, but these effects were more pronounced for NAs because they experienced more pain-related anxiety.

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toward facilitation (disinhibition). Thus, brain-to-spinal cord (descending) mechanisms may disinhibit spinal neurons when pain-related anxiety is high. This could increase pain risk.

It is worth noting that pain-related anxiety mediated the relationship between NA race and CPM of NFR, but not CPM of pain. This is likely a result of separate neural mechanisms that mediate these processes. An fMRI study found that CPM-related changes in pain are likely due to a corticocortical circuit, whereas CPM-related changes in NFR involves a corticospinal circuit. The current study suggests that pain-related anxiety may have an effect on the corticospinal circuit in NAs, without affecting the corticocortical circuit. This implies that pain-related anxiety allows a greater ascending barrage of nociceptive signals through to supraspinal centers. Interestingly, the subjective experience of those signals may still be inhibited, given the lack of mediation for CPM of pain.

It is currently unknown whether a greater ascending nociceptive barrage may still result in negative sequelae, although pain experience is dampened, but recent evidence from our lab suggests this might be the case. Preliminary analyses of OK-SNAP follow-up data suggest that 16% of participants have gone on to develop chronic pain (defined as pain lasting $\geq 3$ months that does not remit at future follow-ups). Analyses show that CPM of NFR, but not CPM of electric pain, predicts this transition. However, these preliminary findings should be interpreted with caution until verified after all 5-year follow-up data are collected.

A fourth implication is that the mechanisms that promote NA pain may be different than other minorities. Race/ethnicity is known to contribute to pain and chronic pain prevalence, but most studies have focused on African-American and Hispanic populations. These generally find that these groups have lower pain tolerances and report more pain in response to supra-threshold stimuli than NHWs. This has been hypothesized to stem, in part, from augmented pain amplification processes (enhanced TS-Pain) and less effective pain inhibitory processes (eg, CPM). By contrast, we do not find that NAs generally differ from NHWs on these measures. Rather, this study suggests that pain-related anxiety is one factor that...
promotes a racial/ethnic difference for NAs. Notably, these findings are not likely due to an anxiety-related response bias because CPM of NFR was affected.

Given that pain-related anxiety appears to be a promoter of spinal facilitation and hyperalgesia (lower tolerance) in NAs, this implies that targeting pain-related anxiety may reduce pain risk by eliminating or minimizing these downstream pronociceptive effects (Fig. 3). Luckily, a number of cognitive-behavioral treatments (CBTs) exist that reduce pain-related anxiety/ fear, and a few studies have also demonstrated that brief CBT can increase descending inhibition of spinal nociception. This study suggests CBTs that target anxiety may be particularly relevant for preventing and/or treating pain in NAs. In addition, evidence suggests that anxiety is associated with the release of cholecystokinin (CCK) that in turn promotes hyperalgesia, thus CCK antagonists (eg, proglumide) may help reduce pain-related anxiety’s pronociceptive effects in NAs.

### 4.2. Potential limitations

We only recruited healthy, pain-free participants, so we cannot generalize our findings to clinical populations, including those with chronic pain. It is possible that pain-related anxiety has different relationships with pronociceptive processes in clinical samples. Moreover, the levels of anxiety may differ in clinical populations, perhaps equalizing groups on this variable and obscuring/eliminating the mediation effects we noted. We also used stringent inclusion criteria that might have excluded persons at the greatest risk for pain and altered the observed relationships. That said, it did not seem to eliminate the higher pain risk in NAs, because our follow-up screens suggest NAs are developing chronic pain at higher rates than NHWs. Our NA sample was drawn mostly from tribes in the northeastern Oklahoma region where most NAs are not reservation-dwelling. It is not clear whether our results will generalize to NAs from other geographical regions, particularly those living on reservations where access to health care may be more limited. Moreover, there are likely to be important cultural variables that differ across NAs from different regions that might alter pain processing (eg, diet, beliefs, and acculturation). And finally, our assessment of pain-related anxiety was limited to a single VAS. This choice was made because we wanted to assess anxiety that was happening in the moment during the painful tasks, rather than rely on reports of how participants experience pain-related anxiety in general. Because we assessed it many times, it had to be brief, and we and others have used this approach successfully in previous studies. Moreover, many of the other measures of pain-related anxiety require respondents to have considerable previous experience with pain and/or chronic pain, and our participants were chronic pain-free. To improve the stability of our pain-related anxiety measurement, we averaged the items from multiple tasks. Despite this, other anxiety measures may produce different results.

### 4.3. Summary

This study examined the impact of pain-related anxiety on measures of pain processing in NAs and NHWs. Mediation analyses indicated that the tendency for NAs to experience greater pain-related anxiety is associated with impaired inhibition of spinal nociception and decreased pain tolerance. Thus, pain-related anxiety may contribute to the pain disparity in NAs.
Disclosures
The authors have no conflicts of interest to declare.

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