Original Reports

Race/Ethnicity Does Not Moderate the Relationship Between Adverse Life Experiences and Temporal Summation of the Nociceptive Flexion Reflex and Pain: Results From the Oklahoma Study of Native American Pain Risk

Cassandra A. Sturycz, Natalie Hellman, Michael F. Payne, Bethany L. Kuhn, Burkhart Hahn, Edward W. Lannon, Shreela Palit, Yvette M. Güereca, Tyler A. Toledo, Joanna O. Shadlow, and Jamie L. Rhudy

Department of Psychology, The University of Tulsa, Tulsa, Oklahoma

Abstract: Adverse life experiences (ALEs) are associated with hyperalgesia and chronic pain, but the underlying mechanisms are poorly understood. One potential mechanism is hyperexcitability of spinal neurons (ie, central sensitization). Given that Native Americans (NAs) are more likely to have ALEs and to have a higher prevalence of chronic pain, the relationship between ALEs and spinal hyperexcitability might contribute to their pain risk. The present study assessed temporal summation of the nociceptive flexion reflex (TS-NFR; a correlate of spinal hyperexcitability) and pain (TS-Pain) in 246 healthy, pain-free non-Hispanic whites and NAs. The Life Events Checklist was used to assess the number of ALEs. Multilevel growth models were used to predict TS-NFR and TS-Pain, after controlling for age, perceived stress, psychological problems, negative and positive affect, and painful stimulus intensity. ALEs and negative affect were significantly associated with greater pain, but not enhanced TS-Pain. By contrast, ALEs were associated with enhanced TS-NFR. Race did not moderate these relationships. This finding implies that ALEs promote hyperalgesia as a result of increased spinal neuron excitability. Although relationships between ALEs and the nociceptive flexion reflex/pain were not stronger in NAs, given prior evidence that NAs experience more ALEs, this factor might contribute to the higher prevalence of chronic pain in NAs.

Perspective: This study found a dose-dependent relationship between ALEs and spinal neuron excitability. Although the relationship was not stronger in NAs than non-Hispanic whites, given prior evidence that NAs experience more ALEs, this could contribute to the higher prevalence of chronic pain in NAs.

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Key words: Temporal summation, nociceptive flexion reflex, adverse life experiences, pain, negative affect, ethnic differences, trauma.
Native Americans (NA) have higher rates of chronic pain than other racial/ethnic groups, but the mechanisms involved in this pain disparity are poorly understood. One psychosocial factor that could contribute is exposure to adverse life events (ALEs; eg, physical/sexual assault). Although much of the work on ALEs has focused on its psychological consequences (ie, posttraumatic stress disorder [PTSD]), ALEs may promote pain in the absence of PTSD. For example, ALE-exposed persons report more pain sites, greater somatization, more negative affect, and poorer perceived health than non-ALE-exposed persons. Given that NAs are more likely to experience ALEs, the ALEs–pain relationship may be particularly relevant for this minority group.

Interestingly, a dose-dependent effect has been found between ALEs and negative sequelae. For example, the number of adverse childhood experiences is associated with worse physical health/quality of life, somatic symptoms, mood/anxiety/stress symptoms, sleep disturbance, anger control, and corticotropin-releasing factor (stress hormone). It is, therefore, possible that a dose-dependent relationship exists between ALEs and pain.

The mechanisms linking ALEs to pain are not well-understood, but one that is emerging is an increased hyperexcitability of nociceptive spinal neurons (ie, central sensitization). A model for studying this was first discovered by Mendell and Wall, who found that repetitive noxious stimuli with an interstimulus interval (ISI) of ≤3-second produced a robust “windup” of dorsal horn neurons in animals. In humans, this is assessed from temporal summation of pain (TS-Pain) and involves the delivery of a train of constant-intensity stimuli that produces increased pain to the last stimulus relative to the first. Although most humans exhibit some TS-Pain, it is enhanced in persons with chronic pain; thus, it is believed that TS-Pain is a marker of the amplification of ascending nociceptive input that promotes chronic pain. Consistent with the notion that ALEs increase spinal cord hyperexcitability, increased TS-Pain has been found in individuals with adverse childhood experiences and patients with a functional gastrointestinal disorder with ALEs (compared with patients with a functional gastrointestinal disorder without ALEs and healthy controls). A potential drawback of TS-Pain stems from the fact that pain ratings are used to make inferences about spinal nociceptive processes. Corticocortical circuits exist that could modulate pain solely at the supraspinal level without altering spinal neurons (eg). This would weaken the correlation between pain report and spinal nociception.

Catastrophizing is associated with TS-Pain, but is unrelated to spinal nociception. A more direct measure of spinal nociception could bolster the argument that ALEs are related to amplification of spinal neurons.

The current study examined the relationship between ALEs and temporal summation of the nociceptive flexion reflex (TS-NFR) and TS-Pain in a healthy, pain-free sample of 281 NAs and non-Hispanic whites (NHWs). The NFR is a spinally mediated nociceptive reflex assessed from an electromyogram (EMG) whose reflex arc does not require supraspinal centers. Thus, the NFR is used as a correlate of spinal nociception. Importantly, NFR magnitude summates in response to a train of noxious stimuli, and animal studies suggest that this factor reflects the hyperexcitability of spinal neurons. As a result, TS-NFR is a more direct measure of spinal neuron hyperexcitability.

It is hypothesized that there will be a dose-dependent relationship between ALEs and TS, such that more ALEs will be associated with greater TS-NFR and TS-Pain. Race/ethnicity was included as a moderator to examine whether the relationship varies in NAs. Although evidence suggests it should be stronger in NAs, a small study of TS-NFR in NAs found that TS-NFR was decreased (not enhanced), relative to NHWs. Thus, it is unclear if the relationship will be stronger or weaker in NAs.

Methods

Participants

All participants (N = 281; 156 women) were healthy, pain-free individuals recruited as part of the Oklahoma Study of Native American Pain Risk (OK-SNAP), a 2-day study investigating risk factors for chronic pain in Native Americans (NAs) and NHWs. NA participants in the current study represent tribal nations predominately from southern plains and eastern Oklahoma tribes. Most NHW and NA participants lived in the Northeastern area of Oklahoma, although recruitment was not limited to this area. All procedures were approved by the Institutional Review Boards of The University of Tulsa, the Cherokee Nation, and the Indian Health Service Oklahoma City Area Office. Participants were recruited via newspaper ads, fliers, email announcements, and online strategies (Facebook, Craigslist). Exclusion criteria included: 1) <18 years old, 2) history of cardiovascular, neuroendocrine, musculoskeletal, or neurologic disorders, 3) current acute or chronic pain, 4) body mass index of ≥35 (owing to difficulties obtaining the NFR), 5) use of an antidepressant, anxiolytic, analgesic, stimulant, or antihypertensive medication, 6) current psychotic symptoms (assessed by the Psychosis Screening Questionnaire) or substance abuse problems, and/or 7) an inability to read/speak English. Participants who identified as NA were required to present verification of their heritage (eg, Certificate of Degree of Indian Blood, tribal affiliation card) to participate.

Participants were given an overview of all procedures and told they could withdraw from the study at any time. All participants provided verbal and written informed consent and received a $100 honorarium for the completion of each testing day (or $10/hour of non-completed days). Of the 281 participants enrolled in the larger study, 246 attended the testing day that included TS and completed some TS testing (see Results for additional sample details).
The present study is an ancillary analysis of data collected to study pain risk in NAs; therefore, the original sample size was not determined \textit{a priori} to power this analysis. However, a sensitivity analysis was conducted to ensure that 246 participants would allow the detection of a meaningful effect size. Based on this $N$ and an $\alpha = .05$, we obtained a power of .80 to detect individual predictors that explain $\geq 3.2\%$ variance in the dependent variables. Notably, this sensitivity analysis is based on less powerful ordinary least squares regression models. The multilevel growth models used will actually exceed this power and will be powered to detect even smaller effects.

\section*{Procedures}

Testing was conducted over a 2-day period, each lasting 4–6 hours. Figure 1 depicts the procedures performed on the temporal summation testing day (note: other outcomes noted in the figure will be reported in subsequent papers). After consent was obtained, a thorough health screening was administered by the experimenter to ensure that all participants were eligible. Once inclusion was established, the Life Events Checklist (LEC) for the \textit{Diagnostic and Statistical Manual of Mental Disorders}, 4th edition, Text Revision, was administered to assess ALEs and then the experimenter applied electrodes and sensors.

Pain tests were pseudorandomized with the exception that the assessment of NFR threshold and the 3-stimulation threshold were always administered first and second, respectively, so that suprathreshold stimulation intensity used during TS testing could be determined (see details elsewhere in this article).

\section*{Power/Sensitivity Analysis}

The present study is an ancillary analysis of data collected to study pain risk in NAs; therefore, the original sample size was not determined \textit{a priori} to power this analysis. However, a sensitivity analysis was conducted to ensure that 246 participants would allow the detection of a meaningful effect size. Based on this $N$ and an $\alpha = .05$, we obtained a power of .80 to detect individual predictors that explain $\geq 3.2\%$ variance in the dependent variables. Notably, this sensitivity analysis is based on less powerful ordinary least squares regression models. The multilevel growth models used will actually exceed this power and will be powered to detect even smaller effects.

\section*{Apparatus, Electrode Application, and Signal Acquisition}

Participants completed all testing in a sound-attenuated and electrically shielded room. Throughout the testing, the experimenter, who was located in an adjacent room, monitored participants via a video camera connected to an LCD television. Participants wore sound-attenuating headphones that provided verbal instructions for each task, and experimenters communicated with participants via a microphone connected to a 40 W audio amplifier (Radio Shack, Fort Worth, Texas; Part #32-2054). All data, questionnaire, and stimuli presentations were controlled by a PC equipped with dual monitors, A/D board (PCI-PCI-6071E; National Instruments, Austin, Texas), and LabVIEW software (National Instruments). One computer monitor presented questionnaires, pain rating scales, and picture stimuli to participants. A second monitor within the control room allowed for the experimenter to evaluate physiologic signals and experimental progress.

An isolated, constant current stimulator (Digitimer DS7A; Hertfordshire, UK) and bipolar stimulating electrode ( Nicolet, 019-401400; Madison, Wisconsin) delivered electrical stimuli to the left ankle over the retromalleolar pathway of the sural nerve. Each stimulus was a train of five 1-ms rectangular wave pulses at 250 Hz. A computer controlled the timing of the electric stimulations (maximum stimulation intensity of 50 mA).

Grass Technologies (West Warwick, Rhode Island), Model 151LT amplifiers (with AC Module 15A54 and Module 15A12) collected and amplified EMG physiologic signals.

Two Ag-AgCl electrodes were placed over the biceps femoris muscle (10 cm superior to the popliteal fossa) to assess EMG associated with NFR. A common ground
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electrode was placed over the lateral epicondyle of the femur. To apply EMG and stimulating electrodes, the skin was first cleaned with alcohol and exfoliated using Nuprep gel (Weaver and Company, Aurora, Colorado) until impedances were <5 kΩ. All electrodes were filled with conductive gel (EC60; Grass Technologies) and applied to the skin via adhesive collars. The signal was sampled at 1000 Hz.

**Questionnaires**

Demographics and Health Exclusion

A custom-made demographics form was used to assess background information for each of the participants (e.g., age, biological sex, socioeconomic status, health status). This information was used to describe the sample as well as to evaluate eligibility criteria.

Adverse Life Experiences

The LEC was used to assess ALEs. It includes 17 items assessing various stressful events: natural disaster, fire/explosion, transportation accident, serious accident at work/home/etc, exposure to toxic substance, physical assault, sexual assault, other unwanted sexual contact, combat exposure, captivity, life-threatening illness, severe human suffering, sudden violent death, sudden unexpected death of someone close, serious harm/death you caused to someone else, and other stressful event. The respondent indicates the range of proximity to the event by assessing if the event “happened to me,” “witnessed it,” or “learned about it.” The authors of the measure have shown that it is a reliable source for assessing ALEs, with test–retest agreement ranging from moderate to substantial. This scale was used to assess ALEs, with test–retest agreement ranging from moderate to substantial.35 This scale was used to assess ALEs, with test–retest agreement ranging from moderate to substantial.35 This scale was used to assess ALEs, with test–retest agreement ranging from moderate to substantial.35 This scale was used to assess ALEs, with test–retest agreement ranging from moderate to substantial.35 This scale was used to assess ALEs, with test–retest agreement ranging from moderate to substantial.35

The subscale ranges from 20-80, with higher scores indicating greater current anxiety.

Psychological Problems

The Symptom Checklist-90-Revised (SCL-90-R) was used to assess psychological problems. The scale consists of 90 items that assess various psychological symptoms. The Global Severity Index (GSI) of the SCL-90-R was used to assess overall psychological problems. Scores range from 0 to 4 with higher scores indicating more problems.

Health Perceptions

The general health perceptions subscale of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) was used to assess perceptions of physical health. Furthermore, the bodily pain subscale was used to assess the degree of pain and interference owing to pain that has occurred over the past 4 weeks (before the first testing day). For both scales, scores are standardized to range from 0 to 100, with higher scores indicating better physical functioning.

Pain Catastrophizing

Pain catastrophizing was assessed using the 13-item Pain Catastrophizing Scale (PCS). Scores for the Pain Catastrophizing Scale ranged from 0 to 52, with higher scores indicating greater catastrophic thoughts.

Pain Ratings

After each electrocutaneous stimulation, participants rated the pain they experienced using a computer-presented visual analog scale (VAS), similar to ones used in prior research. Anchors corresponded with “no pain” and “the most intense pain imaginable,” and the computer converted the scores to numerical values between 0 and 100. Before testing, participants were trained by the experimenter on how to use the pain rating scales through both verbal instructions and a demonstration.

**Determination of Stimulus Intensity for Temporal Summation Testing**

To determine the suprathreshold stimulation intensity used during temporal summation testing, the NFR threshold and 3-stimulation threshold were first assessed. The stimulus intensity was set at 120% of NFR threshold or 120% of 3-stimulation threshold, whichever was higher (in mA). We have previously shown that this ensures that NFRs are reliably elicited throughout testing.66 However, because the stimulus intensity is set at a physiologic threshold, rather than a perceptual threshold (e.g., pain threshold), this introduces more interindividual variability in the perception of the stimulus (but more consistency in the size of the NFR magnitude). Because NFR threshold and 3-stimulation threshold assess spinal nociception, they can also be...
used to assess the static (tonic) reactivity of the spinal cord to painful input, whereas TS-NFR assesses the dynamic (summative) reactivity of the spinal cord to painful input.

Assessment of the NFR Threshold

Three ascending—descending staircases of electric stimuli determined NFR threshold. The first ascending—descending staircase began at 0 mA and increased in 2-mA steps until an NFR was detected. NFR was defined as a mean biceps femoris EMG response within the 90- to 150-ms poststimulus interval that exceeded the mean biceps femoris EMG activity within the 60-ms baseline interval before the delivery of electric stimulus by ≥1.4 standard deviations. After the detection of the first NFR, the electrical current decreased in 1-mA steps until an NFR was no longer detected (trough). The second and third ascending—descending staircases were detected using 1-mA steps. The stimulus intensity (mA) that elicited the 2 NFRs and 2 troughs of the last 2 ascending—descending staircases were averaged and comprised the NFR threshold. In between electrical stimulations, a time interval of ≥8 seconds but not >12 seconds was used to decrease predictability and habituation.

3-Stimulation Threshold Assessment

One ascending staircase, beginning at 0 mA and increasing in 2-mA steps, of 3 electric stimulations (.5-second ISI, 2.0 Hz) were delivered until an NFR was evoked by the third stimulus. The stimulus intensity at which the NFR was evoked was recorded as the 3-stimulation threshold.

TS-Pain and TS-NFR

Five trains of 3 suprathreshold stimuli (.5-second ISI) were used to assess temporal summation. After each train of stimuli, participants were instructed to rate the pain intensity for all 3 stimulations, using a set of 3 computer-presented VASs. After the participant completed the ratings, there was an intertrain interval of 8-12 seconds. The baseline EMGs in the 60 ms before the third stimulus in the stimulus train were visually inspected in real-time by the experimenter for excessive muscle tension or voluntary movement. If the mean rectified EMG was >5 μV, the train was repeated to ensure that EMG activity in the poststimulus interval was not contaminated by muscle tension unrelated to the NFR. NFR magnitudes in response to each stimulus in the 3-stimulus train were calculated in d-units by first subtracting the 60-ms baseline before 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 2 intervals. Note that the poststimulus interval used here differs from our assessment of NFRs in response to single stimuli (ie, 90–150 ms after the stimulus) because repeated stimulations with a short (.5-second) ISI can result in a shorter NFR onset latency.

Data Analysis

Before analyses, variables were examined for non-normality. Skewed distributions were transformed (ie, log10 for right skew). Also, outliers were identified according to Wilcox's recommended MAD-median procedure with the criteria set to 2.24. Identified outliers were winorized to the nearest nonoutlier value. The alpha level was set to $P < .05$ (2-tailed) for all analyses.

Group differences on background characteristics were analyzed using independent t-tests (continuous variables) or $\chi^2$ tests (categorical variables). Ordinary least squares regression analyses were used to predict NFR threshold and 3-stimulation threshold from race, ALEs, and the interaction of Race × ALEs after controlling for age, sex, perceived stress, psychological problems (SCL-90-R GSI subscale), negative affect, and positive affect.

For primary analyses, multilevel growth models were conducted with pain ratings or NFR magnitudes as the dependent variable. Data for these models were kept in long form, meaning that each participant had multiple rows of data that corresponded to each stimulation they received. TS testing involved 5 trains of 3 stimulations; therefore, each participant had 15 rows of data. Thus, participants served as level 2 units in the models and stimulations served as level 1 units. The within-subject variance covariance structure was modeled as a first-order autoregressive matrix (AR1) to account for the significant autocorrelation in the repeated measures. A variable called stimulus number (Stim1, Stim2, Stim3) was entered into these models as a continuous predictor to model the slope of temporal summation (ie, the change in pain/NFR across the 3 stimulations in a train). Train number was also entered as a predictor to account for variance in pain/NFR across the 5 trains. Control variables that were entered included age, sex, perceived stress, psychological problems, negative affect, positive affect, and suprathreshold stimulus intensity. (Note: Based on a reviewer’s recommendation, we also examined bodily pain as a control variable, but it was not a significant covariate in the model for TS-Pain [$P = .335$] or the model for TS-NFR [$P = .96$]. Further, including it did not change any of the conclusions; thus, it is not reported in the final models.) Adverse life experiences (ALEs), race, and their interactions with stimulus number were the primary predictors of interest. All continuous variables were centered by subtracting the grand mean to reduce multicollinearity and aid interpretation. Categorical variables were contrast coded (race: NHW = -1, NA = 1; sex: male = -1, female = 1). The models included a random intercept and a random slope for stimulus number (to allow summation to vary across participants). Finally, the intercepts and slopes were allowed to covary to control for the law of initial values (ie, pain/NFR that is higher in response to the first stimulus is less likely to increase across the 3 stimuli, and vice versa). The $\chi^2$ difference tests were used to determine whether the models were significantly different from a no predictor model (akin to the omnibus F-test used in ordinary least squares linear regression).
To test our primary hypotheses, the main effects of ALEs and race examined whether these variables were associated with overall levels (ie, the intercept) of pain/NFR. The interactions of ALEs $\times$ Stimulus Number and Race $\times$ Stimulus Number tested whether ALEs or race (respectively) were associated with TS-pain or TS-NFR. The ALEs $\times$ Race $\times$ Stimulus Number interaction tested whether the relationship between ALEs and TS differed in NAs.

Results

Final Sample

A total of 281 NA and NHW participants were enrolled in the study; however, only 246 had data available for analysis. Two participants’ data were lost owing to a computer malfunction, 19 completed the first day of testing but did not return for the second day that included TS testing, and 14 completed some testing but quit before TS testing.

Table 1 reports the characteristics for those participants available for analysis and those who were not (this does not include the 2 persons with lost data). As shown, the only significant difference was in state anxiety at the beginning of the physiology testing day. Those without TS data had slightly lower anxiety. There were also trends for persons available for TS analyses to have higher psychological distress, higher perceived stress, and be of younger age, but these did not reach statistical significance at $P < .05$.

The characteristics of the 128 NHW and 118 NA participants with available data are presented in Table 2. NAs had a higher body mass index, reported more psychological problems, required a higher suprathreshold stimulus intensity to evoke NFRs during TS testing (owing to a higher NFR threshold), were more likely to be female, and more likely to cohabitate ($P = .021$) than NHW participants. There was also a trend for NAs to experience more ALEs ($P = .087$).

During data processing/data cleaning, it was noted that 11 participants (4 NHW males, 2 NHW females, 3 NA males, and 2 NA females) had to be excluded from the NFR analyses owing to excess movement during testing. Eight participants (3 NHW males, 2 NA males, and 3 NA females) were excluded from pain rating analyses because all stimuli were rated at the highest level (ie, 100; creating a ceiling effect for TS-Pain).

Variable Conditioning

The ALE variable suffered from outliers. After winsorizing, the new range was 0–5 ALEs. Perceived stress also required winsorizing. Age, negative affect, and psychological distress (SCL-90 GSI) were all right skewed; so, they were log transformed ($\log_{10}$).

ALE Exposure

In the present study, 80% of participants reported experience $\geq 1$ ALE. The percentage of persons reporting individual ALEs were: natural disaster (24%), fire/explosion (12%), transportation accident (48%), serious accident (11%), exposure to toxins (2%), physical assault (25%), assault with weapon (9%), sexual assault (7%), unwanted sexual experience (13%), combat exposure (1%), captivity ($<1$%), life-threatening illness (2%), severe human suffering (1%), sudden violent death (2%), sudden unexpected death (33%), caused serious injury/harm/death (3%), and other (19%).
NFR Threshold and the 3-Stimulation Threshold

The regression model predicting NFR threshold was significant $F(9, 232) = 1.925; P = .049$; however, the only significant predictor in the model was age ($B = .125; P = .038$). Race ($B = 1.460; P = .206$), ALEs ($B = .311; P = .510$), and the interaction ($B = .111; P = .802$) were all nonsignificant. The regression model predicting 3-stimulation threshold was nonsignificant, $F(9, 232) = .528; P = .854$, and no individual predictor was significant (all $P > .25$).

TS-Pain

To briefly summarize findings, pain summated across the 3 stimuli in the trains; however, this summation was not related to ALEs or race. Nonetheless, more ALEs and greater negative affect were associated with greater overall pain during TS-Pain (but not pain summation).

Figure 2 depicts the variance in slopes and intercepts for TS-Pain. Table 3 reports the results of the multilevel growth model analysis for pain and confirms that the variance in intercepts and slopes is significant.

Table 2. Characteristics of NA and NHW individuals with available TS data

<table>
<thead>
<tr>
<th>Continuous Variable</th>
<th>NHW ($n = 128$)</th>
<th>NA ($n = 118$)</th>
<th>t</th>
<th>P VALUE</th>
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<tr>
<td>Age, y</td>
<td>28.281</td>
<td>30.661</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>7.895</td>
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<td>.296</td>
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<td>ALEs (0-17)</td>
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<td>3.621</td>
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<td>Negative affect (PANAS; 0-40)</td>
<td>3.407</td>
<td>3.762</td>
<td>-2.728</td>
<td>.007</td>
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<td>Positive affect (PANAS; 0-40)</td>
<td>1.918</td>
<td>1.961</td>
<td>-2.984</td>
<td>.003</td>
</tr>
<tr>
<td>State anxiety (STAI; 0-20)</td>
<td>3.486</td>
<td>3.762</td>
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<td>Perceived stress (PSS; 0-40)</td>
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<td>3.407</td>
<td>-2.984</td>
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<tr>
<td>Psychological problems (SCL-90; 0-4)</td>
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<td>General health scale (SF-36; 0-100)</td>
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<td>7.895</td>
<td>-2.984</td>
<td>.003</td>
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<tr>
<td>Bodily pain subscale (SF-36; 0-100)</td>
<td>3.407</td>
<td>3.762</td>
<td>-2.984</td>
<td>.003</td>
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<tr>
<td>NFR threshold (0–50mA)</td>
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<td>1.961</td>
<td>-2.984</td>
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<tr>
<td>3-Stimulation threshold (0–50mA)</td>
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<td>1.961</td>
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<table>
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<th>Categorical Variables</th>
<th>NHW</th>
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<th>%</th>
<th>$\chi^2$</th>
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<td>13%</td>
<td>12%</td>
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<td>46%</td>
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<td>27%</td>
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<td>9</td>
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<td>8%</td>
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<td>&gt;40 h/wk</td>
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<td>34</td>
<td>22%</td>
<td>29%</td>
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<td>&lt;40 h/wk</td>
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<td>47%</td>
<td>38%</td>
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<td>4%</td>
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<td>36</td>
<td>27%</td>
<td>31%</td>
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<td>Income</td>
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<td>&lt;$9999</td>
<td>47</td>
<td>30</td>
<td>37%</td>
<td>27%</td>
<td>7.874</td>
<td>.163</td>
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<tr>
<td>$10,000–$14,999</td>
<td>15</td>
<td>11</td>
<td>12%</td>
<td>10%</td>
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<tr>
<td>$15,000–$24,999</td>
<td>16</td>
<td>17</td>
<td>13%</td>
<td>15%</td>
<td>7.874</td>
<td>.163</td>
</tr>
<tr>
<td>$25,000–$34,999</td>
<td>11</td>
<td>15</td>
<td>9%</td>
<td>13%</td>
<td>7.874</td>
<td>.163</td>
</tr>
<tr>
<td>$35,000–$49,999</td>
<td>10</td>
<td>19</td>
<td>8%</td>
<td>17%</td>
<td>7.874</td>
<td>.163</td>
</tr>
<tr>
<td>&gt;$50,000</td>
<td>27</td>
<td>21</td>
<td>21%</td>
<td>19%</td>
<td>7.874</td>
<td>.163</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.771</td>
<td>.021</td>
</tr>
<tr>
<td>Single</td>
<td>97</td>
<td>72</td>
<td>76%</td>
<td>62%</td>
<td>9.771</td>
<td>.021</td>
</tr>
<tr>
<td>Married</td>
<td>21</td>
<td>22</td>
<td>16%</td>
<td>19%</td>
<td>9.771</td>
<td>.021</td>
</tr>
<tr>
<td>Separated/divorce/widowed</td>
<td>8</td>
<td>13</td>
<td>6%</td>
<td>11%</td>
<td>9.771</td>
<td>.021</td>
</tr>
<tr>
<td>Cohabitating</td>
<td>2</td>
<td>10</td>
<td>2%</td>
<td>9%</td>
<td>9.771</td>
<td>.021</td>
</tr>
</tbody>
</table>

Abbreviations: M, mean; SD, standard deviation; PCS, Pain Catastrophizing Scale; PANAS, Positive and Negative Affect Schedule; STAI, State Trait Anxiety Inventory; PSS, Perceived Stress Scale; SF-36, Medical Outcomes Study Short Form, 36-item; NFR, Nociceptive Flexion Reflex.

NOTE. Items in bold are statistically significant.
The \( \chi^2 \) difference test indicated that the model was statistically significant, \( \Delta \chi^2 (df = 17) = 849.10; P < .001. \) There was significant summation of pain as indicated by the main effect of stimulus number \( (P < .001), \) but this was not moderated by race or ALEs. Nonetheless, the main effect of ALEs \( (P = .026) \) indicates that more ALEs is associated with higher pain (Fig 3). There was also a significant main effect of negative affect \( (P = .029), \) indicating that greater negative affect is also associated with more pain (Fig 3).

The main effect of stimulus intensity \( (P < .001) \) reflects that persons receiving a higher stimulus experienced more pain. The main effect of train number \( (P < .001) \) shows that pain increased across the 5 trains.

### Table 3. Results of multilevel growth curve analysis for TS-Pain

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intercept</td>
<td>48.729*</td>
<td>1.755</td>
<td>45.275</td>
<td>52.184</td>
</tr>
<tr>
<td>Suprathreshold stimulus intensity</td>
<td>.610*</td>
<td>.159</td>
<td>.297</td>
<td>.922</td>
</tr>
<tr>
<td>Train number</td>
<td>1.545*</td>
<td>.239</td>
<td>1.074</td>
<td>2.015</td>
</tr>
<tr>
<td>Stimulus number</td>
<td>1.637*</td>
<td>.241</td>
<td>1.163</td>
<td>2.111</td>
</tr>
<tr>
<td>Female sex</td>
<td>.668</td>
<td>1.715</td>
<td>-2.711</td>
<td>4.048</td>
</tr>
<tr>
<td>Age</td>
<td>.883</td>
<td>11.749</td>
<td>-22.621</td>
<td>24.025</td>
</tr>
<tr>
<td>Negative affect (PANAS)</td>
<td>15.366*</td>
<td>5.789</td>
<td>3.961</td>
<td>26.770</td>
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<tr>
<td>Perceived stress (PSS)</td>
<td>-415</td>
<td>396</td>
<td>-1.196</td>
<td>.365</td>
</tr>
<tr>
<td>Psychological problems (SCL-90)</td>
<td>16.429</td>
<td>29.282</td>
<td>-41.256</td>
<td>74.114</td>
</tr>
<tr>
<td>Positive affect (PANAS)</td>
<td>-408</td>
<td>233</td>
<td>-4.67</td>
<td>.451</td>
</tr>
<tr>
<td>Race</td>
<td>917</td>
<td>1.740</td>
<td>-2.510</td>
<td>4.345</td>
</tr>
<tr>
<td>ALEs</td>
<td>2.426*</td>
<td>1.172</td>
<td>.118</td>
<td>4.735</td>
</tr>
<tr>
<td>Stim Number ( \times ) Race</td>
<td>-.041</td>
<td>.231</td>
<td>-.497</td>
<td>.415</td>
</tr>
<tr>
<td>Stim Number ( \times ) ALEs</td>
<td>.053</td>
<td>.144</td>
<td>-.231</td>
<td>.338</td>
</tr>
<tr>
<td>Race ( \times ) ALEs</td>
<td>-.806</td>
<td>1.063</td>
<td>-2.901</td>
<td>1.289</td>
</tr>
<tr>
<td>Stim Number ( \times ) Race ( \times ) ALEs</td>
<td>.065</td>
<td>.144</td>
<td>-.219</td>
<td>.350</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR1 diagonal</td>
<td>163.878*</td>
<td>21.256</td>
<td>127.091</td>
<td>211.313</td>
</tr>
<tr>
<td>AR1 rho</td>
<td>.863*</td>
<td>.018</td>
<td>.822</td>
<td>.894</td>
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<tr>
<td>Stimulus number intercept variance</td>
<td>585.298*</td>
<td>63.681</td>
<td>472.895</td>
<td>724.418</td>
</tr>
<tr>
<td>Intercept and slope covariance</td>
<td>-1.582</td>
<td>6.086</td>
<td>-13.510</td>
<td>10.346</td>
</tr>
<tr>
<td>Stimulus number slope variance</td>
<td>10.614*</td>
<td>1.148</td>
<td>8.586</td>
<td>13.121</td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error of coefficient/estimate; CI, confidence interval; PANAS, Positive and Negative Affect Schedule; PSS, Perceived Stress Scale; AR1, first-order autoregressive structure.

**NOTE:** Estimates are unstandardized relationships between the predictors and the dependent variable. Estimates in **bold** text are significant at \( *P < .05. \) Sex was coded as -1 for male and 1 for female. Race was coded as -1 for NHW and 1 for NA.
Results from the random effects in Table 3 show that there is still significant variance in the intercepts and slopes to be explained (all \( P < .001 \)), but that intercepts and slopes were unrelated (\( P = .795 \)). This last fact indicates that the degree of TS-Pain was unrelated to the initial pain level evoked by the first stimulus in the series (e.g., more TS-Pain was not due to lower pain ratings to the first stimulus).

Temporal Summation of NFR

To briefly summarize our findings, more ALEs were associated with greater TS-NFR. Race did not moderate this relationship, suggesting that the effect of ALEs on NFR is similar in NA and NHW groups. Figure 2 depicts the variance in slopes and intercepts for TS-NFR. Table 4 reports the results of the multilevel growth model analysis for NFR and confirms that the variance in intercepts and slopes is significant.

Table 4. Results of multilevel growth curve analysis for TS-NFR

<table>
<thead>
<tr>
<th></th>
<th>( \text{ESTIMATE} )</th>
<th>( \text{SE} )</th>
<th>( \text{LOWER} )</th>
<th>( \text{UPPER} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed effects</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.205*</td>
<td>.028</td>
<td>1.150</td>
<td>1.260</td>
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<tr>
<td>Suprathreshold</td>
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<td>.002</td>
<td>-.005</td>
<td>.004</td>
</tr>
<tr>
<td>Stimulus intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Train number</td>
<td>-.020*</td>
<td>.005</td>
<td>-.029</td>
<td>-.010</td>
</tr>
<tr>
<td>Stimulus number</td>
<td>.268*</td>
<td>.017</td>
<td>.234</td>
<td>.301</td>
</tr>
<tr>
<td>Female sex</td>
<td>-.031</td>
<td>.026</td>
<td>-.083</td>
<td>.020</td>
</tr>
<tr>
<td>Age</td>
<td>.080</td>
<td>.178</td>
<td>-.270</td>
<td>.430</td>
</tr>
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<td>Negative affect (PANAS)</td>
<td>.039</td>
<td>.089</td>
<td>-.137</td>
<td>.214</td>
</tr>
<tr>
<td>Perceived stress (PSS)</td>
<td>.006</td>
<td>.006</td>
<td>-.006</td>
<td>.018</td>
</tr>
<tr>
<td>Psychological problems (SCL-90)</td>
<td>-.294</td>
<td>.461</td>
<td>-.120</td>
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</tr>
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<td>.004</td>
<td>-.006</td>
<td>.008</td>
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<td>Race</td>
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<tr>
<td>ALEs</td>
<td>.022</td>
<td>.018</td>
<td>-.014</td>
<td>.058</td>
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<tr>
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<td>.019</td>
<td>.017</td>
<td>-.015</td>
<td>.053</td>
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<tr>
<td>Stim Number ( \times ) ALEs</td>
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<td>.011</td>
<td>.006</td>
<td>.049</td>
</tr>
<tr>
<td>Race ( \times ) ALEs</td>
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<td>.017</td>
<td>-.047</td>
<td>.019</td>
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<tr>
<td>Stim Number ( \times ) ALEs</td>
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<td>.011</td>
<td>-.032</td>
<td>.011</td>
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<tr>
<td><strong>Random effects</strong></td>
<td></td>
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</tr>
<tr>
<td>AR1 diagonal</td>
<td>.132*</td>
<td>.004</td>
<td>.125</td>
<td>.139</td>
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<td>AR1 rho</td>
<td>.094*</td>
<td>.020</td>
<td>.055</td>
<td>.133</td>
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<td>Stimulus number</td>
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<td>.015</td>
<td>.120</td>
<td>.178</td>
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<tr>
<td>Intercept variance</td>
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<td></td>
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<tr>
<td>Intercept and slope covariance</td>
<td>.023*</td>
<td>.007</td>
<td>.009</td>
<td>.037</td>
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<tr>
<td>Stimulus number slope variance</td>
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<td>.006</td>
<td>.043</td>
<td>.068</td>
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</table>

Abbreviations: SE, standard error of coefficient/estimate; CI, confidence interval; PANAS, Positive and Negative Affect Schedule; PSS, Perceived Stress Scale; AR1, first-order autoregressive structure.

NOTE: Estimates are unstandardized relationships between the predictors and the dependent variable.

NOTE: Estimates are unstandardized relationships between the predictors and the dependent variable.

Estimates in bold text are significant at *\( P < .05 \). Sex was coded as -1 for male and 1 for female. Race was coded -1 for NHW and 1 for NA.

Figure 4. The predicted relationship between ALEs and TS-NFR. Individual (simple) regression lines are based on the multilevel growth curve model. NFRs increased over the 3-stimulus train, indicating a temporary hyperexcitability of spinal neurons. However, persons who experienced a higher number of ALEs had greater TS-NFR, suggesting enhanced hyperexcitability (central sensitization) of spinal neurons in these individuals. This could serve as a risk factor for future chronic pain.
The $\chi^2$ difference test indicated that this model was statistically significant, $\Delta \chi^2 (df = 17) = 1267.27; P < .001$. There was significant summation of NFR as noted by the main effect of stimulus number ($P < .001$), but this effect was moderated by ALEs ($P = .012$). Specifically, persons reporting more ALEs experienced greater TS-NFR (see Fig 4 and Fig 5). Race was unrelated to NFR ($P = .781$) and the summation of NFR ($P = .265$), and it did not moderate the relationship between ALEs and the summation of NFR ($P = .346$).

The main effect of train number ($P < .001$) shows that NFR magnitudes decreased across the 5 trains.

Results from the random effects in Table 4 show that there is still significant variance in the intercepts and slopes to be explained (all $P < .001$), and the intercepts and slopes were related ($P = .012$). The significant covariance between the intercept and slope suggests that the degree of TS-NFR was related to the initial NFR magnitude evoked by the first stimulus in the series and underscores the importance of controlling for this issue.

**Discussion**

This study examined the relationships between ALEs and TS-NFR and TS-Pain. As predicted, ALEs were associated with enhanced TS-NFR, suggesting that exposure to ALEs promotes spinal neuron hyperexcitability in a dose-dependent manner. Although ALEs were not associated with enhanced TS-Pain, they were associated with higher pain ratings, suggesting that they promote hyperalgesia. The relationships between ALEs and pain/NFR were not moderated by race, indicating that NASs and NHWs did not differ. Notably, these relationships were not explained by age, negative affect, positive affect, sex, stress, or psychological problems because these variables were controlled in the models. Of the control variables, only negative affect was found to be a significant predictor of pain. Although ALEs were associated with TS-NFR, they were not associated with the NFR threshold or the 3-stimulation threshold. The implications are discussed herein.

**ALEs May Promote Central Sensitization and Hyperalgesia**

Central sensitization is believed to promote the onset and maintenance of many chronic pain conditions (eg, fibromyalgia). Although TS-Pain/TS-NFR and windup (the animal analog) are not synonymous with central sensitization, TS-NFR and TS-Pain are believed to assess physiologic processes important to central sensitization, such as the activity of $N$-methyl-$D$-aspartate (NMDA) receptors and spinal neuron hyperexcitability. Moreover, past research has found that enhanced TS-Pain and TS-NFR are associated with chronic pain. We found that ALEs exert a dose-dependent influence on TS-NFR (more ALEs = greater NFR summation). This indicates persons with more ALEs have greater hyperexcitability of spinal neurons. Although TS-NFR, the NFR threshold, and the 3-stimulation threshold all measure aspects of spinal nociception, ALEs were not associated with the NFR threshold or the 3-stimulation threshold. This finding likely reflects the underlying physiologic mechanisms responsible. The NFR...
threshold and the 3-stimulation threshold are assumed mediated by \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainite receptors (AMPA)\(^6,\)\(^91,\)\(^101\) whereas TS-NFR is mediated by NMDA receptors.\(^6,\)\(^36\) Thus, ALEs may have a stronger effect on NMDA-related mechanisms (ie, central sensitization).

Notably, these effects were found in healthy, pain-free persons; therefore, ALEs may place individuals at future risk for chronic pain by promoting central sensitization. Interestingly, ALEs were not associated with enhanced TS-Pain. Rather, ALEs seem to promote general hyperalgesia, because those that participants who reported more ALEs experienced more overall pain in response to the electric stimuli. Together, it seems that ALEs may be a risk factor for pain because they promote central sensitization and hyperalgesia.

**Exposure to ALEs May Contribute to NAs Pain Disparities**

Prior studies have found that NAs have a higher prevalence of chronic pain than NHWs and other racial/ethnic minorities.\(^6,\)\(^25\) However, a few small prior studies found that NAs have higher pain thresholds/tolerances (ie, hypalgesia)\(^6,\)\(^56,\)\(^71\) and decreased TS-NFR.\(^6,\)\(^57\) We previously speculated that this could represent a risk factor that is unique to NAs,\(^6,\)\(^56,\)\(^71\) because other racial/ethnic minorities at a high chronic pain risk show the opposite pattern (eg, hyperalgesia, higher TS-Pain).\(^6,\)\(^1\)\(^2\) To better understand the mechanisms contributing to NA pain, we implemented the OK-SNAP, from which the current data were drawn. Thus far, findings from OK-SNAP are not consistent with those prior studies. Instead, we find that, similar to other minority groups, NAs have lower pain tolerances (hyperalgesia) and report more pain-related negative affect in response to painful stimuli.\(^55,\)\(^6,\)\(^4\)

Relative to NHW, the current results indicate that NAs do not 1) report more pain in response to electric stimuli, 2) have enhanced TS-NFR or TS-Pain, or 3) show a stronger relationship between ALEs and TS-NFR/TS-Pain. That said, ALEs may nonetheless represent an important pain risk pathway for NAs. Indeed, considerable evidence suggests that ALEs are more prevalent in NAs,\(^6,\)\(^10,\)\(^13,\)\(^40,\)\(^42,\)\(^43,\)\(^47,\)\(^60,\)\(^73,\)\(^74\) which is consistent with the marginally higher rate we observed. Given this finding, the higher base rate of ALEs may help to explain a higher rate of chronic pain in this population. Longitudinal studies are necessary to confirm this, but, if true, then pharmacologic (eg, NMDA antagonists)\(^6,\)\(^54\) and/or nonpharmacologic (eg, cognitive-behavioral therapy)\(^6,\)\(^71,\)\(^77,\)\(^89\) interventions that reverse central sensitization could be used after exposure to ALEs to prevent the future chronic pain development.

**Negative Affect May Contribute to NA Pain Disparities**

Consistent with prior studies,\(^44,\)\(^4,\)\(^50,\)\(^68,\)\(^69\) we found that negative affect was associated with greater pain. Moreover, the relationship between negative affect and pain was found to be independent of the effect of ALEs on pain. Thus, our findings are consistent with a study that showed negative mood and ALEs independently predicted the progression from acute back pain to later disability.\(^1\)\(^5\) Taken together, greater negative affect may independently contribute to hyperalgesia and chronic pain risk.\(^44,\)\(^4,\)\(^68,\)\(^95\)

As noted, we have found that NAs experience more negative affect in response to painful stimuli.\(^55,\)\(^6,\)\(^4\) If this finding is also true of their response to clinical pain, as it is with other minorities,\(^72\) then a negative affect may provide an additional pathway to pain risk for this population. Given that the relationship between negative affect and TS-Pain/TS-NFR was not a central aim of the present study, we did not formally test whether the negative affect and pain relationship was moderated by race. Nonetheless, we explored this interaction and it was nonsignificant (data not shown). Taken together, negative affect and ALEs may exert independent effects on pain processing and both may promote pain risk in NAs.

**Why Do ALEs Influence TS-NFR, But Not TS-Pain?**

The TS-NFR assesses spinal nociception.\(^79\) Thus, it should provide some insight into the pain signals relayed to the brain to produce pain perception. However, NFR and pain can diverge, because there are multiple modulatory circuits. For example, some are local (eg, spinal–spinal, corticocortical) and some descend from supraspinal centers (cerebrospinal).\(^27,\)\(^59,\)\(^75,\)\(^78\) Consistent with this notion, some psychosocial factors influence pain and TS-Pain, but not NFR or TS-NFR (eg, catastrophizing).\(^22,\)\(^29,\)\(^32,\)\(^34,\)\(^66,\)\(^87\) whereas others influence pain and NFR similarly (eg, emotions).\(^62,\)\(^71\) Thus, our findings suggest that ALEs promote spinal neuron hyperexcitability that amplifies ascending nociceptive input to promote general hyperalgesia, without leading to enhanced TS-Pain.

That said, these results should be interpreted with caution until they are replicated. Indeed, the divergence between TS-NFR and TS-Pain could have stemmed from ceiling effect. Given that those with higher ALEs already reported greater pain, it may have limited the amount of pain summation that could occur. However, this notion was not supported by our finding that the covariance between the model intercept (initial pain rating) and the slope (degree of pain summation) was nonsignificant.

Alternatively, our failure to see enhanced TS-Pain could have resulted from the way pain was assessed. Electric stimulations were delivered with a .5-second ISI, so participants did not have time to make ratings between stimuli. Rather, they rated all 3 stimuli after the 3-stimulus train. As a result, exposure to the third stimulus may have biased their ratings of earlier stimuli. Although this factor may have impacted our measurement of TS-Pain, it is not likely to have affected our measurement of pain more generally. So, our finding that ALEs and negative affect are associated with hyperalgesia remains valid. Moreover, this would not have affected our primary aim, which was to examine the relationship between ALEs and TS-NFR.
Adverse Events and Temporal Summation of NFR

Adverse Events and Temporal Summation of NFR

The Journal of Pain

Strengths and Limitations

This study is the first to examine the relationship between ALEs and TS-NFR in a large sample of NA and NHW men and women. Additionally, statistically powerful analyses were used to model the data complexity and control for potential confounds. Nonetheless, a few additional limitations should be noted.

First, the LEC limited the information gathered about ALEs. Similar to the commonly used Adverse Childhood Experiences questionnaire, the LEC only provides the number of different events that a person experiences. It does not assess the event’s severity, the person’s reaction, or its chronicity/repetition. Further, the LEC does not assess for some less severe events or others adverse childhood experiences (e.g., divorce, job loss) that might be important. Thus, future research is needed to examine the influence of ALEs not assessed by the LEC. Second, psychological diagnoses were not obtained, so we are unable to determine if clinically significant distress impacted our results, or whether these results generalize to clinical samples (e.g., PTSD). Third, this study recruited healthy, pain-free subjects to examine the effect of ALEs before pain onset, so it is unclear whether these results generalize to chronic pain samples. Finally, future studies are needed to determine whether augmented TS-NFR and hyperalgesia ultimately promote future chronic pain. However, preliminary analyses of OK-SNAP follow-up data suggest this.37

Summary

These findings imply that ALEs have a dose-dependent effect on central sensitization (as assessed by TS-NFR) and hyperalgesia. This finding is independent of perceived stress, negative/positive affect, sex, age, and psychological symptoms. Only negative affect emerged as an independent predictor of pain. Although these relationships were not moderated by race, they could nonetheless contribute to the greater prevalence of chronic pain in NAs, because prior studies have noted that NAs are more likely to experience ALEs and pain-related negative affect.

References


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