



# The Relationship Between Adverse Life Events and Endogenous Inhibition of Pain and Spinal Nociception: Findings From the Oklahoma Study of Native American Pain Risk (OK-SNAP)

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**Abstract:** Adverse life events (ALEs) are a risk factor for chronic pain; however, mechanisms underlying this association are not understood. This study examined whether cumulative ALE exposure impairs endogenous inhibition of pain (assessed from pain report) and spinal nociception (assessed from nociceptive flexion reflex; NFR) in healthy, pain-free Native Americans (n = 124) and non-Hispanic Whites (n = 129) during a conditioned pain modulation (CPM) task. Cumulative ALE exposure was assessed prior to testing by summing the number of potentially traumatic events experienced by each participant across their lifespan. Multilevel modeling found that ALEs were associated with NFR modulation during the CPM task even after controlling for general health, body mass index, sex, age, blood pressure, sleep quality, stimulation intensity, stimulus number, perceived stress, and psychological distress. Low exposure to ALEs was associated with NFR inhibition, whereas high exposure to ALEs was associated with NFR facilitation. By contrast, pain perception was inhibited during the CPM task regardless of the level of ALE exposure. Race/ethnicity did not moderate these results. Thus, ALEs may be pronociceptive for both Native Americans and non-Hispanic Whites by impairing descending inhibition of spinal nociception. This could contribute to a chronic pain risk phenotype involving latent spinal sensitization.

**Perspective:** This study found that adverse life events were associated with impaired descending inhibition of spinal nociception in a sample of Native Americans and non-Hispanic Whites. These findings expand on previous research linking adversity to chronic pain risk by identifying a proximate physiological mechanism for this association.

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**Key words:** Adverse life events, nociceptive flexion reflex, conditioned pain modulation, trauma, pain.

Accumulating evidence suggests a dose-dependent relationship between ALEs and myriad negative sequelae, including sleep disturbances,<sup>1</sup> immune dysregulation,<sup>31</sup> somatic problems,<sup>1</sup> lower

quality of life,<sup>1</sup> and psychopathology.<sup>17</sup> ALEs are also considered to be a risk factor for chronic pain,<sup>52,70</sup> yet few proximate mechanisms have been identified to explain the link. Nonetheless, the cumulative number of

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ALEs is associated with pain risk above and beyond the severity and magnitude of each individual event.<sup>67,70</sup>

Yarnitsky et al. (2014) have argued that greater pain facilitation (assessed by temporal summation [TS]) and impaired endogenous pain inhibition (assessed by conditioned pain modulation [CPM]) promote risk for chronic pain. TS measures the extent to which repeated noxious stimuli amplify pain,<sup>64</sup> an effect that is believed due to spinal neuron hyperexcitability (ie, wind-up in animals).<sup>37</sup> Some have found that TS of pain (TS-pain) is enhanced in people reporting more ALEs.<sup>68</sup> Furthermore, greater ALE exposure is associated with enhanced TS of the nociceptive flexion reflex (TS-NFR), a withdrawal reflex used to assess spinal nociception.<sup>46,55</sup> This supports the notion that ALEs increase spinal neuron hyperexcitability in a dose-dependent manner.<sup>55</sup> Consistent with this, other studies have found that ALEs were associated with greater capsaicin-induced secondary hyperalgesia/allodynia (markers of spinal sensitization).<sup>68,69</sup> These studies suggest ALEs may increase risk for chronic pain by amplifying spinal nociception,<sup>39</sup> but the effect on endogenous inhibition is less clear.

Endogenous mechanisms exist that allow CNS inhibition of spinal nociception.<sup>2,29,41,58</sup> When impaired, incoming nociceptive signals are more likely to be experienced as painful and thus could promote chronic pain.<sup>2,58</sup> The CPM task compares the degree to which a painful test stimulus is inhibited by a painful conditioning stimulus at a distal location. In humans, CPM-related pain inhibition (CPM-pain) is typically assessed using self-report pain ratings, and thus may not exclusively reflect descending inhibition of spinal nociception.<sup>41,51</sup> Nonetheless, CPM can inhibit the spinally-mediated NFR,<sup>12,29</sup> so the effect of the CPM task on NFR (CPM-NFR) can be used to assess descending inhibition of spinal nociception. To our knowledge, only one study has examined the link between adversity and CPM-NFR and found that a specific type of adversity (ie, sexual assault) was associated with disrupted CPM-NFR inhibition.<sup>22</sup> Thus, it is plausible that ALEs may confer a dose-dependent pain risk by increasing spinal hyperexcitability (TS-NFR)<sup>55</sup> and impairing inhibition of spinal nociception (CPM-NFR).

Moreover, establishing the relationship between ALEs and chronic pain risk may improve our understanding of pain disparities among racial/ethnic minorities. For example, African-Americans experience considerable ALEs,<sup>36,53</sup> and also suffer from a significant pain disparity.<sup>38,45</sup> Their pain disparity may at least partially result from impaired CPM-pain inhibition,<sup>6</sup> perhaps due to exposure to adversity. Similarly, Native Americans (NAs) are more likely to experience ALEs than non-Hispanic whites (NHWs)<sup>33</sup> and are more likely to experience chronic pain.<sup>25</sup> Thus, ALEs could promote pronociceptive mechanisms (e.g., enhanced TS, impaired CPM) contributing to higher rates of chronic pain in NAs. However, it is unclear whether ALEs have a dose-dependent effect on CPM-related inhibition, and whether this effect is stronger in NAs. To address these issues, data from healthy, pain-free NAs and NHWs who participated in the Oklahoma Study of Native American Pain

Risk (OK-SNAP) were analyzed. It was hypothesized that ALEs would be associated with impaired CPM-NFR and CPM-pain. Given that NAs have a higher risk of chronic pain, we also hypothesized that the effect of ALEs on CPM would be stronger in NAs. However, it is also possible that the effect of ALEs on CPM is similar in NAs and NHWs given that race/ethnicity did not moderate the effect of ALEs on TS.<sup>55</sup>

## Methods

### Participants

OK-SNAP was a 2-day study designed to assess risk factors (eg, pain sensitivity, measures of central sensitization, and measures of endogenous inhibition) for chronic pain in NAs. Pain-free NA and NHW participants were recruited so that risk factors for chronic pain could be identified prior to the onset of disease when racial/ethnic differences could be confounded by differences in disease severity, access to health care, or other factors. Data were collected from March 2014 through October 2018.

Out of the 329 found eligible in OK-SNAP, 2 participants' data were lost due to a computer malfunction, 22 participants were non-NA minorities and thus were excluded from analyses, and 3 were later excluded for having type 1 or type 2 diabetes. This resulted in 302 participants in the final sample. Of these, 253 (120 men) completed some or all of CPM and are used in the current study (differences between completers and non-completers are reported in the Results section and Table 1). Papers reporting on the racial/ethnic group differences in pain sensitivity, central sensitization, and endogenous inhibition (without considering ALEs) can be found elsewhere.<sup>49,50</sup> A subset of these data were used to explore the relationship between sexual assault and CPM (prior to completion of data collection in OK-SNAP),<sup>22</sup> but the current hypotheses and analyses were novel in that they: 1) tested a dose-dependent relationship between cumulative ALE exposure and CPM (regardless of ALE type) and 2) examined whether race/ethnicity moderates the ALEs-CPM relationships.

Prior to performing any study procedures, all participants provided verbal and written informed consent. As compensation, each participant received \$100 per testing day completed. If a subject withdrew during a testing day, they received \$10 for each hour completed that day. All study procedures were approved by the Institutional Review Boards at the University of Tulsa, the Cherokee Nation, and the Indian Health Service Oklahoma City Area Office. Participants were recruited via fliers, newspaper ads, emails, Craigslist ads, Facebook ads, and in person meetings with NA groups.

The study excluded people who were younger than 18 years old, people with a history of cardiovascular, neuroendocrine, musculoskeletal, or neurological disorders, people with acute or chronic pain, people who were unable to read or write fluently in English, and people with a body mass index (BMI) greater than or equal to 35 (due to difficulties recording NFR). People

**Table 1. Comparison of Participants with and without CPM Data on Continuous Background Variables**

CONTINUOUS VARIABLE	COMPLETED CPM (N=251)		DID NOT COMPLETE CPM (N=51)		T	P	COHEN'S D
	M	SD	M	SD			
Age (years)	28.928	12.796	32.882	14.271	1.834	0.071	0.303
Adverse Life Events (ALEs)	2.084	1.612	2.000	1.575	-0.345	0.731	-0.052
Body Mass Index (kg/m <sup>2</sup> )	24.920	4.232	25.492	4.158	0.891	0.376	0.136
Mean Arterial Pressure (mmHg)	85.274	9.149	86.901	7.968	1.251	0.215	0.181
Dispositional Pain Catastrophizing (PCS; 0–52)	9.624	7.573	9.143	7.853	-0.394	0.695	-0.063
Negative Affect (PANAS; 0–40)	2.900	2.604	2.939	2.520	0.098	0.922	0.015
Positive Affect (PANAS; 0–40)	18.536	7.275	19.235	8.326	0.338	0.740	0.095
State Anxiety (STAI; 20–80)	32.736	7.098	31.694	7.335	-0.914	0.364	-0.146
SCL-90 – Global Severity Index (0–4)	0.125	0.087	0.096	0.082	-2.223	0.041	-0.331
Perceived Stress (PSS; 0–40)	13.852	6.005	13.326	6.031	-0.529	0.599	-0.088
SF-36 Body Pain Scale (0–100)	90.200	10.802	93.023	8.139	1.993	0.050	0.270
SF-36 General Health Scale (0–100)	79.480	13.765	79.070	14.811	-0.169	0.866	-0.029
Subjective Sleep Quality (0–3)	1.106	0.764	1.167	0.753	0.194	0.853	0.079

Abbreviations: PCS, Pain Catastrophizing Scale. PANAS, Positive and Negative Affect Schedule. STAI, State Trait Anxiety Inventory. SCL-90, Symptom Checklist 90. PSS, Perceived Stress Scale. SF-36, Medical Outcomes Short Study Form, 36-item.

who used antidepressant, anxiolytic, stimulant, or anti-hypertensive medications within four half-lives of the respective drug prior to testing were also excluded. Use of over-the-counter analgesics was exclusionary if used within 24 hours of testing, and use of prescription analgesics was exclusionary if used within two weeks prior to testing. Additionally, people who endorsed having current psychotic symptoms or substance abuse were excluded. NA participants were required to provide verification of their tribal affiliation for inclusion in the NA group (eg, Certificate of Degree of Indian Blood Card, tribal affiliation card). NA participants in the current study represent tribal nations predominately from the southern plains and eastern Oklahoma tribes. To respect tribal confidentiality, tribal affiliations are not reported.

### Testing Day Procedures

OK-SNAP consisted of two testing days that each lasted approximately 4–6 hours. For a detailed overview of all OK-SNAP procedures, see,<sup>50</sup> and for a detailed description of the CPM day procedures, see.<sup>57</sup> To briefly summarize, participants provided informed consent and then sensors were applied for recording NFR. Following sensor application, participants completed questionnaires (ie, dispositional catastrophizing, PANAS, STAI) before undergoing procedures to determine the electric test stimulus intensity used during the CPM task (NFR threshold, Pain30 [Pain30 was only administered if NFR threshold stimuli did not evoke pain that was at least a 30 out of 100 on a VAS], and 3-stimulation threshold).

Afterwards, participants underwent a battery of pain tasks (responses to heat pulses, single electric stimulations, and TS-NFR) and then completed the SF-36 questionnaire. Finally, participants underwent CPM and emotional controls of nociception (ECON) tasks, the order of which was randomized. The SCL-90 and PSS

were completed between these two tasks. Mandatory breaks were taken after tasks to reduce the likelihood of carryover effects.

### Apparatus, Electrode Application, and Signal Acquisition

All procedures were controlled on a dual monitor computer using an analog-to-digital board (USB-6212 BNC; National Instruments, Austin, TX, USA) with LabVIEW software (National Instruments). Study procedures took place in a sound-attenuated and electrically shielded experiment room, and participants used a monitor and computer mouse to complete electronic questionnaires, except that pain ratings were made verbally during CPM testing. Additionally, participants wore sound-attenuating headphones to communicate with the researcher and to receive pre-recorded instructions. While testing occurred, researchers in an adjacent control room monitored the participant physiology that was displayed on a second monitor. To ensure protocol compliance, researchers monitored participants during tasks using a video camera.

At the beginning of the CPM testing day, a medical grade device (Dinamap; Tampa, FL) was used to measure mean arterial pressure (MAP) 3 times at rest with 3-minute intervals between each test. The average MAP of these three readings was used as a control variable in the current analyses since NAs experienced slightly higher blood pressure than NHWs.

### Conditioned Pain Modulation (CPM)

Similar to prior research, the CPM paradigm used cold water as the conditioning stimulus (CS) and an electric stimulation as the test stimulus.<sup>26,32</sup> The paradigm involved 3 phases (baseline, conditioning, posttest)

lasting 2-minutes each. Each phase began with a 20-second waiting period. During the baseline phase, participants were exposed to 5 electrical stimulations delivered at an interstimulus interval of 8–12 seconds. After each stimulation, participants were instructed to verbally report the pain felt due to the stimulation between 0–100 on a numerical rating scale (NRS) with anchors every 20 points (0=no pain, 20=mild pain, 40=moderate pain, 60=severe pain, 80=very severe pain, 100=worst possible pain).<sup>50</sup> At the end of the baseline phase, participants rested for 2-minutes before beginning the conditioning phase, at which point they were instructed to submerge their right hand (palms down, fingers spread) into painfully cold  $10 \pm 0.1^\circ\text{C}$  water CS up to their forearm.<sup>32</sup> During the 2-minutes of hand submersion, 5 electrical stimulations (test stimuli) were delivered at an interstimulus interval of 8-12 seconds. Participants gave verbal pain ratings in response to each stimulation using the same 0–100 NRS used during the baseline phase. After a 5-min rest period, participants began the posttest phase (data not presented), which was identical to the baseline phase. Following the posttest phase, participants were instructed to use the NRS to rate the pain they experienced due to the cold water. All test stimuli were set at the highest of 1.2x NFR threshold,  $1.2 \times 3$ -stimulation threshold, or 1x Pain30 (described below). Experimenters recorded the participants' verbal ratings in response each stimulation, which were used for CPM-pain analyses. NFR magnitude was measured in response to each stimulation and was used for CPM-NFR analyses.

### Conditioning Stimulus (CS)

A regulated  $10 \pm 0.1^\circ\text{C}$  cold water bath was used as the CS during CPM (Thermo Fisher Scientific, Pittsburgh, PA). Participants were asked to submerge their right hand up to their forearm in the cold water for 2 minutes. They were instructed to place their palm face-down and spread their fingers during CPM conditioning. On average, the CS evoked moderate to severe pain (mean NRS rating = 54) and ratings did not differ by ethnic group (Table 2).

### Test Stimuli

A constant current nerve stimulator (Digimeter DS7A; Hertfordshire, England) and a bipolar electrode (Nicolet, Model #019-40400, Madison, WI, USA) that was placed on the left ankle over the retromalleolar pathway of the sural nerve, was used to deliver electric stimuli. The timing of stimulations was controlled by computer. All stimulations were delivered as trains of five 1-ms rectangular wave pulses at 250-Hz; these were perceived as a single stimulus. To ensure participant safety, the stimulus intensity of electric stimulations was capped at 50-mA.

### NFR Recording

NFR activity was measured using electromyography (EMG) of the left biceps femoris, which is located

approximately 10-cm superior to the popliteal fossa. To record this activity, two Ag-AgCl electrodes were placed over the left biceps femoris, where signals were recorded, filtered (10-Hz–300-Hz), and amplified ( $\times 10,000$ ) using a Grass Technologies (West Warwick, RI, USA) Model 15LT amplifier (with AC Module 15A54). A ground electrode was also placed on the lateral epicondyle of the femur. Prior to sensor and stimulating electrode application, a researcher cleaned the participant's skin with alcohol and exfoliated (NuPrep gel; Weaver and Company, Aurora, CO, USA) before a conductive gel (EC60, Grass Technologies) was placed onto all electrodes and sensors to achieve impedances  $\leq 5\text{k}\Omega$ . NFR magnitude was calculated using a d-score (NFR  $d = [\text{mean rectified EMG of } 90\text{-}150\text{ ms poststimulation interval} - \text{mean of rectified EMG from } -60\text{ to } 0\text{ ms prestimulation interval}] / \text{average standard deviation of the rectified EMG from the } 2\text{ intervals}$ ).

### NFR Threshold

To determine the intensity of the CPM test stimulus, NFR threshold was determined according to three ascending-descending staircases method.<sup>46</sup> Beginning at 0 mA, participants underwent a single electric stimulation that increased in 2 mA increments until an NFR was detected, which occurred when the rectified EMG activity in the 90–150 ms poststimulus interval was 1.4 standard deviations greater than the rectified EMG activity in the -60-0 ms prestimulus interval. After obtaining the first NFR, the stimulations decreased in 1 mA intervals until an NFR was no longer detected. Then, the second and third ascending-descending staircases obtained NFRs using 1 mA increments. The current study defined NFR threshold as the average stimulus intensity (mA) of the peaks and troughs obtained during the second and third ascending-descending staircases.

### Pain30

During the staircases of NFR threshold, participants also rated the pain caused by the electric stimulations using the visual analog scale (VAS), which ranged from 0 (no pain) to 100 (maximum tolerable pain). If the average VAS rating of NFR threshold was not greater than or equal to 30, stimulations continued and increased at 2 mA increments until this rating was obtained (Pain30).

### 3-Stimulation Threshold

Following NFR threshold and Pain30 testing, a 3-stimulation NFR threshold was obtained. Beginning at 0-mA and increasing by 2-mA increments, a series of 3 electric stimulations was delivered with an interstimulus interval of 0.5 seconds until an NFR was elicited on the last stimulus in the series.

## Questionnaires

### Demographics and Health Exclusion

As part of the screening process and to provide descriptive information of the sample, participants

**Table 2. Comparison of Non-Hispanic white (NHW) and Native American (NA) Participants on Background Variables**

CONTINUOUS VARIABLE	NHW (N=129)		NA (N=124)		T	P	COHEN'S D
	M	SD	M	SD			
Age (years)	28.519	13.569	29.339	11.925	-0.509	0.611	0.064
Adverse Life Events (ALEs)	1.754	1.473	2.139	1.602	-1.970	0.050	0.250
Body Mass Index (kg/m <sup>2</sup> )	24.210	3.757	25.717	4.570	-2.845	0.005	0.361
Mean Arterial Pressure (mmHg)	82.459	7.268	88.300	9.819	-5.333	<0.001	0.676
Dispositional Pain Catastrophizing (PCS; 0–52)	9.806	7.562	9.545	7.604	0.274	0.785	0.034
Negative Affect (PANAS; 0–40)	2.806	2.613	3.057	2.625	-0.760	0.448	0.096
Positive Affect (PANAS; 0–40)	17.938	6.875	19.114	7.669	-1.283	0.201	0.162
State Anxiety (STAI; 20–80)	32.411	6.903	33.146	7.288	-0.823	0.411	0.104
SCL-90 – Global Severity Index (0–4)	0.336	0.332	0.445	0.416	-3.059	0.002	0.291
Perceived Stress (PSS; 0–40)	13.039	5.631	14.697	6.265	-2.207	0.028	0.279
SF-36 Body Pain Scale (0–100)	91.221	9.708	89.184	11.247	1.543	0.124	0.142
SF-36 General Health Scale (0–100)	81.047	13.385	78.033	13.504	1.881	0.061	0.294
Subjective Sleep Quality (0–3)	0.948	0.630	1.268	0.849	-3.219	0.001	-0.429
Suprathreshold Stimulus Intensity (0–50mA)	25.034	12.558	27.425	12.156	-1.538	0.125	0.193
Cold Water Pain (0–100)	51.820	24.266	55.910	24.281	-1.334	0.184	0.168

CATEGORICAL VARIABLE	N	%	N	%	χ <sup>2</sup>	P
Sex (male)	65	50.4%	55	44.4%	0.923	0.337
Education					2.890	0.409
High School Graduate or Less	15	11.7%	22	17.9%		
Some College	68	53.1%	54	43.9%		
College Graduate	34	26.6%	36	29.3%		
Graduate/Professional School	11	8.6%	11	8.9%		
Employment					3.863	0.145
≥40 h per Week	28	22.0%	39	32.0%		
<40 h per Week	60	47.2%	45	36.9%		
Retired	39	30.7%	38	31.1%		
Income					9.491	0.091
<\$9,999	49	38.6%	30	25.0%		
\$10,000–\$14,999	15	11.8%	15	12.5%		
\$15,000–\$24,999	16	12.6%	15	12.5%		
\$25,000–\$34,999	10	7.9%	15	12.5%		
\$35,000–\$49,999	10	7.9%	21	17.5%		
≥\$50,000	27	21.3%	24	20.0%		
Marital Status					5.553	0.062
Single	97	75.2%	79	64.8%		
Married	22	17.1%	22	18.0%		
Other	10	8.8%	21	17.2%		

Abbreviations: NHW, non-Hispanic white. NA, Native American. PCS, Pain Catastrophizing Scale. PANAS, Positive and Negative Affect Schedule. STAI, State Trait Anxiety Inventory. SCL-90, Symptom Checklist 90. PSS, Perceived Stress Scale. SF-36, Medical Outcomes Short Study Form, 36-item.

provided background information (eg, sex, age, SES, and health status). In addition, height and weight were measured using a medical scale to calculate BMI.

**Psychological Problems**

Psychological problems were measured using the Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R). The SCL-90-R consists of 90 questions that broadly address different areas of psychopathology (eg, somatic complaints, obsessive-compulsive symptoms, depression, phobic anxiety, paranoia, and psychoticism), and it has been widely utilized across treatment and research settings.<sup>11,43</sup>

**Perceived Stress**

The Perceived Stress Scale (PSS), a 10 item measure assessing perceived stress in the past month, was given to participants. Scores range from 0–40; higher scores are indicative of more perceived stress.<sup>8</sup>

**Perceptions of Physical Health**

The General Health (11 items) and Body Pain (2 items) subscales of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) were used to measure participants' physical health.<sup>60</sup> Scores on each subscale range from 0–100, and lower scores broadly indicate worse health.<sup>60</sup> Specifically, lower scores on the General



Health subscale suggest that an individual believes that their health is generally poor and that it is unlikely to improve,<sup>60</sup> and low scores on the Body Pain subscale suggest that an individual experiences severe and/or disabling pain.<sup>60</sup>

### Perceived Sleep Quality

Subjective sleep quality was assessed using the sleep quality item of the Pittsburgh Sleep Quality Index (PSQI).<sup>5</sup> Participants rated their sleep quality during the past month on a scale of 0 (very good) to 3 (very bad).

### Adverse Life Events (ALEs)

To assess ALEs, the Life Events Checklist (LEC) for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision, was administered.<sup>4</sup> The LEC is a self-report measure containing 17 items asking participants whether they have directly experienced, witnessed, learned about, or have not heard about various ALEs in their lifetime; each item assesses a single stressful or traumatic event. The LEC has been found to be a reliable and valid measure of exposure to potentially traumatic events.<sup>19</sup> In the current study, ALEs were operationally defined as having direct exposure (answering “happened to me”) to any items on the LEC, with a possible range of 0–17. The distribution of scores for ALEs was highly skewed, primarily driven by outliers in the positive direction. To address this, outliers were winsorized to the nearest non-outlier value (ie, 5), so the winsorized ALE variable ranged from 0 to 5 (see description of outlier detection in the Data Analysis section).

### Data Analysis

All analyses were performed using SPSS v25. Before being analyzed, all variables were first examined for non-normality, and skewed distributions were corrected using transformations. Outliers were identified using Wilcoxon's<sup>61</sup> MAD-median procedure using a cutoff of 2.24 and were winsorized to the nearest non-outlier value. An alpha level of  $P < .05$  (two-tailed) was used in all analyses. To determine between-group differences between NAs and NHWs, independent samples t-tests were conducted on continuous variables; variables demonstrating group differences were grand mean centered and used as control variables in the model. Categorical variables were analyzed using chi-square analyses.

For the primary analyses, the current study compared data from the baseline and conditioning phases of CPM (the only conditions needed to assess descending inhibition) using regression-based multilevel models. Multilevel models are advantageous because they can simultaneously model the intra- and inter-individual variance in subjective reactions (ie, pain ratings) and physiological responses (ie, NFR magnitudes).<sup>47</sup> Thus, each repeated observation of the primary dependent variables (ie, verbal pain ratings for CPM-pain, NFR magnitude for CPM-NFR) served as a level 1 unit and was given its own row, such that each participant (level 2

unit) who completed the baseline and conditioning phases of CPM had 10 rows of data (1 row for each stimulation). A first-order autoregressive matrix (AR1) was used to model the within-subject variance-covariance structure in order to account for autocorrelations across repeated measures. Since a regression-based approach was taken, all predictors were treated as if they were continuous-like. The primary independent variable in this study, CPM phase, was dummy coded 0 (baseline) and 1 (conditioning) and used as a continuous-like predictor in order to code for the slope of CPM-related modulation, which varied across level 2 units (participants). The ALEs variable was entered as a continuous-like variable and was centered at 3 so that the interaction term could be created between ALEs and CPM phase without causing multicollinearity. Stimulus number (Stim1 to Stim5) which coded for the 5 stimulations in each CPM phase was entered as a continuous-like control variable to account for habituation/sensitization in response to electric stimuli delivered during CPM. Interactions between CPM phase and ALEs were tested to determine whether inhibition during CPM was affected by the number of ALEs endorsed by each participant. Additionally, race/ethnicity was coded as a continuous-like predictor (-1 = NHW, 1 = NA), and a three-way interaction was tested to determine whether race/ethnicity moderated the relationship between ALEs and CPM phase. In the event of a significant ALEs x CPM phase interaction, simple effects for CPM phase were calculated for each of the low, medium, and high values of the ALE variable (ie, 0, 3,  $\geq 5$ )<sup>42</sup> to evaluate the effect of ALE exposure on the CPM effect.

## Results

### Sample Characteristics

Of the enrolled participants, 29 did not attend any of the CPM testing day, and 23 of the enrolled participants attended the CPM testing day but withdrew prior to CPM. Only one participant dropped out during the CPM task because of the pain from the cold water. See [Table 1](#) for differences between CPM completers and non-completers. The final sample of participants with some CPM data totaled 253 (129 NHW, 124 NA).

Of the participants with CPM data, 52 (20 NAs) reported 0 ALEs, 61 (33 NAs) reported 1 ALE, 58 (27 NAs) reported 2 ALEs, 38 (17 NAs) reported 3 ALEs, 19 (11 NAs) reported 4 ALEs, and 24 (16 NAs) reported  $\geq 5$  ALEs. One NHW did not complete the LEC.

Characteristics of the 129 NHW and 124 NA participants are presented in [Table 2](#). Although the differences between NAs and NHWs on exposure to ALEs did not reach statistical significance ( $P = .05$ ), it was in the predicted direction and represents a 22% greater exposure to ALEs within the NA group, which at the population level is clearly significant. Analysis of group differences found that NA participants had higher BMI, higher MAP, higher levels of psychological distress (SCL-90 GSI), and higher perceived stress (PSS).

### Variable Conditioning

For the current analyses, psychological problems (GSI) were log transformed due to positive skew. Outliers were identified and subsequently winsorized for ALEs (as noted previously), perceived stress (PSS), sleep problems (PSQI), the General Health subscale of the SF-36, NFR magnitudes, and pain ratings. To minimize potential bias in the results, four participants were excluded from CPM-pain analyses due to having CPM baseline pain ratings at ceiling (NRS rating  $\geq 95$ ) or floor (NRS rating  $\leq 5$ ). In addition, individual stimulation trials with an averaged pre-stimulus baseline EMG  $\geq 3\mu V$  (ie, excess muscle tension) were excluded from NFR analysis (4.12% of 2377 trials).

### Control Variables

Given that NAs and NHWs differed on BMI, mean arterial pressure (MAP), subjective sleep quality (PSQI), self-reported psychological distress (SCL-90-R GSI), and perceived stress levels (PSS), these variables were controlled for in the analyses. Further, sex, age, and general health

(general health scale of the SF-36) were also controlled for given their potential influence on CPM.<sup>28,34</sup> And finally, suprathreshold stimulus intensity differed for each participant so it was controlled for in all analyses.

### CPM-NFR

Table 3 reports the results of the multilevel model of NFR and provides summary statistics for our data. Although there was no significant main effect of CPM phase, a significant interaction between ALEs and CPM phase was found ( $P = .003$ ). Consistent with a regression-based approach, Fig 1 depicts CPM-NFR at high (ie,  $\geq 5$ ), medium (ie, 3), and low (ie, 0) ALEs. CPM phase was associated with significant NFR inhibition for people with 0 ALEs ( $P = .001$ ). For people with 3 ALEs, CPM phase was not found to significantly modulate NFR ( $p > .05$ ) (note: because the interaction was significant, the main effect of CPM phase reflects the simple effect of CPM phase when ALEs = 3, due to ALEs being centered at 3). But, for people with  $\geq 5$  ALEs, CPM phase was associated with a significant facilitation of NFR ( $P = .031$ ).

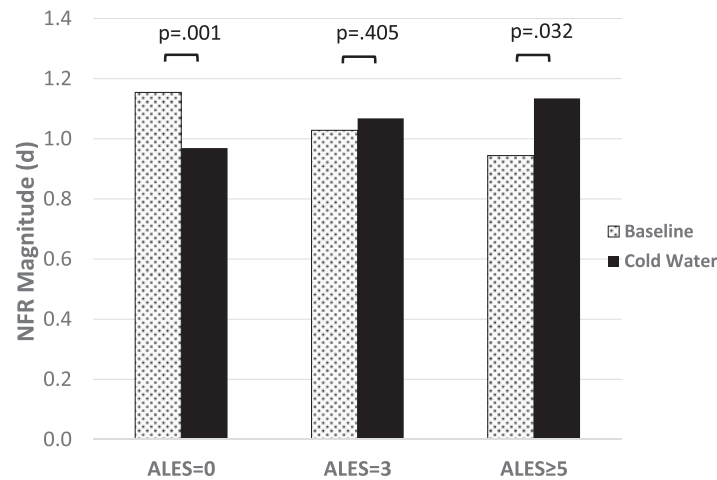
Table 3. Results of Multilevel Growth Curve Analysis of CPM-NFR

FIXED EFFECTS	ESTIMATE	SE	95% CONFIDENCE INTERVAL	
			LOWER	UPPER
Intercept	<b>1.028*</b>	0.071	0.888	1.168
ALEs	-0.042	0.038	-0.116	0.032
CPM Phase	0.040	0.048	-0.053	0.134
Stimulus Number	<b>-0.045*</b>	0.006	-0.057	-0.034
Suprathreshold Stimulus Intensity	<b>0.015*</b>	0.003	0.010	0.021
Age	< -0.001	0.003	-0.006	0.006
Sex	-0.029	0.035	-0.097	0.040
Body Mass Index (kg/m <sup>2</sup> )	-0.003	0.009	-0.021	0.014
Mean Arterial Pressure (mmHg)	-0.005	0.004	-0.014	0.004
Sleep Quality (PSQI)	0.097	0.052	-0.004	0.199
Perceived Stress (PSS)	-0.001	0.009	-0.018	0.016
Psychological Distress (log GSI)	-0.176	0.635	-1.424	1.073
General Health (SF-36-GH)	< -0.001	0.003	-0.007	0.007
Race (NA)	0.027	0.097	-0.163	0.218
ALEs x CPM Phase	<b>0.075*</b>	0.025	0.026	0.124
ALEs x Race (NA)	0.052	0.049	-0.045	0.149
CPM Phase x Race (NA)	-0.014	0.064	-0.140	0.112
ALEs x CPM Phase x Race (NA)	-0.064	0.034	-0.131	0.003

RANDOM EFFECTS	ESTIMATE	SE	95% CONFIDENCE INTERVAL	
			LOWER	UPPER
AR1 diagonal	<b>0.157*</b>	0.006	0.146	0.168
AR1 rho	<b>0.083*</b>	0.030	0.025	0.142
Intercept Variance	<b>0.299*</b>	0.031	0.245	0.365
Intercept and CPM Phase Covariance	<b>-0.064*</b>	0.017	-0.097	-0.031
CPM Phase Variance	<b>0.094*</b>	0.016	0.068	0.130

Note. Estimates show the unstandardized relationship between each predictor and the criterion. Bolded text indicates significance at  $*p < .05$ . Abbreviations: SE, Standard error of estimate/coefficient. PSQI, Pittsburgh Sleep Quality Index. PSS, Perceived Stress Scale. GSI, Global Severity Index of the Symptom Checklist 90. SF-36-GH, General Health Scale of the Short Form Health Survey. NA, Native American. ALEs, Adverse Life Events. CPM, Conditioned Pain Modulation. Sex was coded -1=male and 1=female. Race was coded 0=non-Hispanic white and 1=Native American. AR1=first-order autoregressive structure.



**Fig 1.** Effect of adverse life events (ALEs) on nociceptive flexion reflex (NFR) magnitudes during conditioned pain modulation (CPM). Results suggest a significant interaction between ALEs and pain modulation evoked by the cold water conditioning stimulus (CS) in the CPM paradigm ( $P = 0.003$ ). People with 0 ALEs showed statistically significant inhibition of NFR ( $P = 0.001$ ) when exposed to the CS phase of CPM, whereas people with 5 or more ALEs showed statistically significant facilitation of NFR ( $P = 0.031$ ) when exposed to the CS phase of CPM. People with 3 ALEs showed no statistically significant changes in NFR magnitude in response to the CS phase of CPM.

There were no main effects or interactions with race, indicating the relationship between ALEs and CPM-NFR was statistically equivalent in NAs and NHWs.

The significant main effect of stimulus number ( $P < .001$ ), indicated habituation of NFR within each CPM phase. The significant main effect of stimulus intensity ( $P < .001$ ) indicated that stronger electric stimulations were associated with larger NFRs. The model intercept was significant ( $P < .001$ ) indicating that NFR magnitudes were significantly different from zero when all predictors were controlled.

As for the random effects, the significant diagonal and rho effects indicate that there was significant repeated measures (within-subject) variance and significant across-time covariance in NFR, respectively. The significant intercept variance indicates that there was significant unexplained between-subject variance in NFR during CPM baseline to be explained. The significant CPM phase slope variance indicates that there was significant unexplained between-subject variability in the CPM-related modulation of NFR. And finally, the significant negative covariance between the intercept and CPM phase slope indicates that those with higher NFRs during the CPM baseline were more likely to show greater inhibition of NFR during CPM, and vice versa.

### CPM-pain

Table 4 reports the results of the multilevel model of pain and provides summary statistics for our data. A significant main effect of CPM phase was found ( $P < .001$ ), indicating participants found electrical stimulations to be less painful during the cold water phase of CPM. But unlike CPM-NFR, ALEs did not moderate the relationship between CPM phase and pain ratings (Fig 2). There were also no significant effects containing race, indicating NAs and NHWs did not differ statistically in their pain inhibition.

The significant main effect of stimulus number ( $P < .001$ ) suggested sensitization of pain ratings during each CPM phase. The significant main effect of stimulus intensity ( $P = .016$ ) indicated that higher electrical stimulation intensity was associated with higher pain ratings. Additionally, the significant main effect of psychological distress ( $P = .027$ ) suggested that greater psychological distress was associated with higher pain ratings. The model intercept was significant ( $P < .001$ ) indicating that pain ratings were significantly different from zero when all predictors were controlled.

As for the random effects, the significant diagonal and rho effects indicate that there was significant repeated measures (within-subject) variance and significant across-time covariance in pain ratings, respectively. The significant intercept variance indicates that there was significant unexplained between-subject variance in pain during CPM baseline to be explained. The significant CPM phase slope variance indicates that there was significant unexplained between-subject variability in the CPM-related modulation of pain. And finally, the significant negative covariance between the intercept and CPM phase slope indicates that those with higher pain ratings during the CPM baseline were more likely to show greater inhibition of pain during CPM, and vice versa.

### Discussion

This study was the first to assess whether cumulative ALEs had a dose-dependent relationship with endogenous inhibition of spinal nociception (NFR) and pain in NAs. It was hypothesized that modulation of pain perception and NFR would be associated with ALEs, but ALEs were only associated with NFR modulation. Higher exposure to ALEs was associated with less CPM-NFR inhibition, and even NFR facilitation at high ALEs (Fig 1). Together, these findings suggest ALEs may confer chronic pain risk by disrupting descending



**Table 4. Results of Multilevel Growth Curve Analysis of CPM of Electric Pain Ratings**

FIXED EFFECTS	ESTIMATE	SE	95% CONFIDENCE INTERVAL	
			LOWER	UPPER
Intercept	<b>37.778*</b>	2.029	33.782	41.775
ALEs	1.274	1.068	-0.830	3.377
CPM Phase	<b>-6.420*</b>	1.143	-8.682	-4.158
Stimulus Number	<b>0.753*</b>	0.103	0.550	0.955
Suprathreshold Stimulus Intensity	<b>0.187*</b>	0.075	0.038	0.335
Age	0.144	0.087	-0.026	0.315
Sex	0.948	0.964	-0.949	2.846
Body Mass Index (kg/m <sup>2</sup> )	0.058	0.249	-0.433	0.549
Mean Arterial Pressure (mmHg)	-0.083	0.124	-0.321	0.161
Sleep Quality (PSQI)	-1.801	1.423	-4.604	1.003
Perceived Stress (PSS)	-0.103	0.236	-0.568	0.361
Psychological Distress (log GSI)	<b>35.598*</b>	17.402	1.326	69.871
General Health (SF-36-GH)	-0.139	0.097	-0.329	0.052
Race (NA)	0.227	2.747	-5.183	5.637
ALEs x CPM Phase	-0.568	0.584	-1.722	0.586
ALEs x Race (NA)	-1.358	1.408	-4.131	1.415
CPM Phase x Race (NA)	-1.087	1.502	-4.056	1.882
ALEs x CPM Phase x Race (NA)	0.780	0.799	-0.800	2.359

RANDOM EFFECTS	ESTIMATE	SE	95% CONFIDENCE INTERVAL	
			LOWER	UPPER
AR1 diagonal	<b>71.303*</b>	9.754	54.534	93.228
AR1 rho	<b>0.660*</b>	0.052	0.545	0.751
Intercept Variance	<b>238.585*</b>	25.217	193.944	293.502
Intercept and CPM Phase Covariance	<b>-57.001*</b>	12.077	-80.672	-33.330
CPM Phase Variance	<b>53.967*</b>	10.021	37.503	77.658

**Note.** Estimates show the unstandardized relationship between each predictor and the criterion. Bolded text indicates significance at  $*p < .05$ . Abbreviations: SE, Standard error of estimate/coefficient. PSQI, Pittsburgh Sleep Quality Index. PSS, Perceived Stress Scale. GSI, Global Severity Index of the Symptom Checklist 90. SF-36-GH, General Health Scale of the Short Form Health Survey. NA, Native American. ALEs, Adverse Life Events. CPM, Conditioned Pain Modulation. Sex was coded -1=male and 1=female. Race was coded 0=non-Hispanic White and 1=Native American. AR1=first-order autoregressive structure.

(cerebrospinal) inhibition of spinal nociception without altering pain experience.

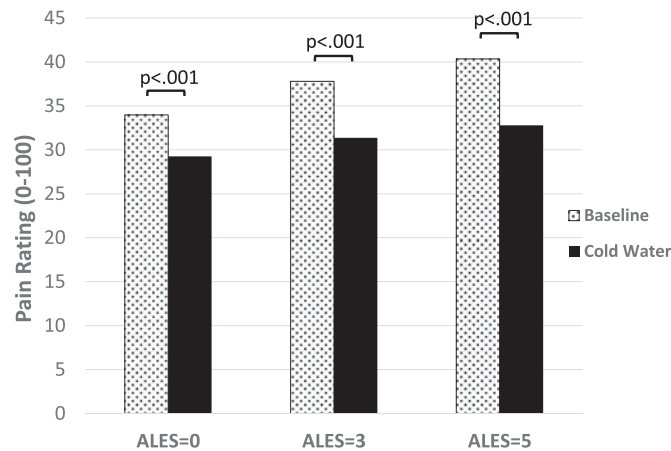
### **Adverse Life Events May Promote Pronociceptive Mechanisms**

Combined with other OK-SNAP findings,<sup>22,55</sup> ALEs appear to promote a pronociceptive phenotype by enhancing TS-NFR and disrupting CPM-NFR. Some have argued that TS and CPM are experimental predictors of chronic pain onset,<sup>66</sup> and 3 studies have prospectively demonstrated CPM's ability to predict future chronic pain. Yarnitsky et al. showed that disrupted CPM-pain (test stimulus = hot thermode on volar forearm, CS = 46.5°C water) prospectively predicted the onset of chronic pain in a sample of 62 thoracotomy patients.<sup>65</sup> Landau et al replicated these findings showing that a pre-surgical CPM assessment in a sample of 75 pregnant women could predict post-Cesarian pain.<sup>27</sup> Finally, less inhibition during CPM with electric and pressure test stimuli and painful cold water CS was found to predict future chronic pain in a study of 20 participants undergoing elective abdominal surgery.<sup>62</sup>

Indeed, CPM-pain appears to be a predictor of chronic pain, and while it does not appear that many studies have used CPM-NFR to predict pain onset, preliminary follow-up data collected from OK-SNAP indicate that CPM-NFR may also predict chronic pain onset, even above and beyond CPM-pain.<sup>23</sup> Given the clinical utility of identifying individuals at risk for developing chronic pain, additional prospective research is warranted. Furthermore, these at-risk individuals may benefit from interventions that specifically increase descending inhibition of spinal nociception, such as relaxation or biofeedback.<sup>14,15,48</sup>

### **ALEs Impact CPM-NFR, but not CPM-Pain: Possible Latent Spinal Sensitization?**

Although NFR and pain are correlated,<sup>7,20,63</sup> they assess different processes. NFR serves as a proxy measure for spinal nociception, whereas pain ratings reflect a combination of incoming spinal nociceptive signaling and supraspinal processing.<sup>29,63</sup> To support this notion,



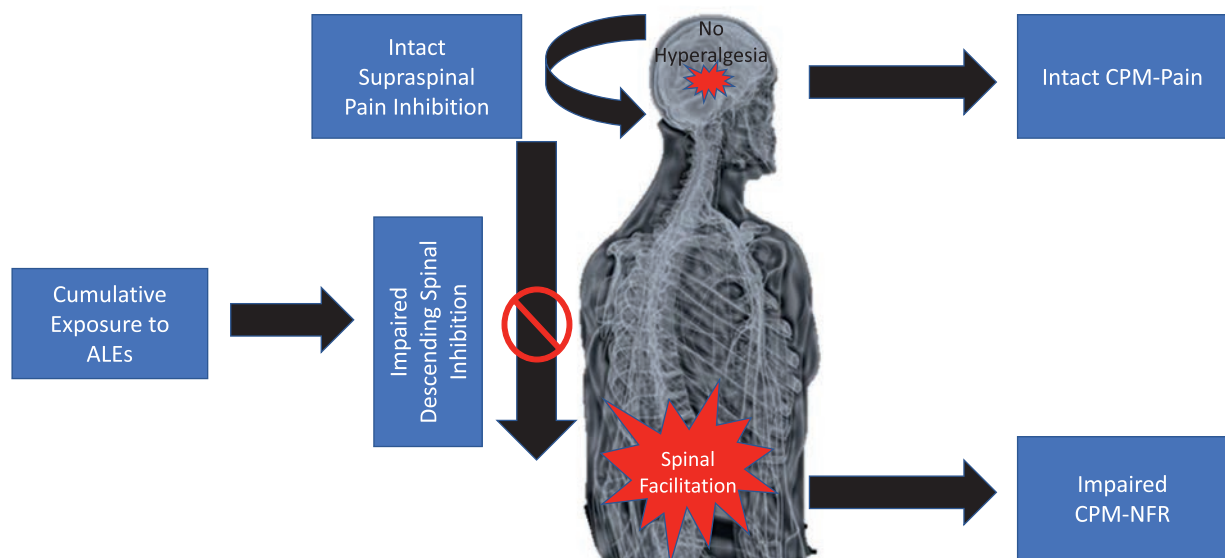
**Fig 2.** Effect of adverse life events (ALEs) on pain ratings during conditioned pain modulation (CPM). ALEs did not moderate the relationship between CPM phase and subjective pain ratings ( $P = .332$ ). Regardless of ALEs, the cold water conditioning stimulus led to significant inhibition of pain ratings.

NFR and pain ratings have been shown to differ under pharmacological<sup>40</sup> and psychological<sup>10</sup> conditions. Furthermore, a study by Piché et al<sup>41</sup> identified distinct neural circuits for CPM-NFR (cerebrospinal circuit) and CPM-pain (fully supraspinal circuit). Thus, a dysfunction in cerebrospinal descending inhibitory circuits that are uniquely associated with NFR inhibition may mediate the dose-dependent association between ALEs and risk for chronic pain.

Given that separate mechanisms may mediate CPM-NFR vs. CPM-pain, then it is possible that CPM-NFR impairment may occur earlier than CPM-pain impairment in a cascade of events that promote chronic pain onset. Indeed, the present study contributes to accumulating evidence that, in healthy, pain-free participants, adversity may promote spinal sensitization without concomitant pain amplification.<sup>21,22,55,68,69</sup> This

apparent disconnect between spinal nociception and pain perception could be explained by intact supraspinal pain inhibitory processes that keep amplified spinal nociception from being experienced as more painful (Fig 3).

This notion is akin to the rodent model of chronic pain vulnerability called *latent sensitization*.<sup>35,44,56</sup> In rodents, exposure to a major stressor or inflammatory insult leads to a sensitization of spinal nociception and hyperalgesia.<sup>9,56</sup> But after a few days, the hyperalgesia remits suggesting the insult has been resolved. However, if an opioid antagonist (eg, naloxone, naltrexone) is administered during the apparent state of remission, the animal returns to a hyperalgesic state, yet animals not exposed to stress or an inflammatory insult do not show this same response to opioid blockade.<sup>56</sup> According to this model, the spinal sensitization that promotes



**Fig 3.** Proposed heuristic model for how adverse life events (ALEs) may confer chronic pain risk in currently healthy, pain-free individuals. Experiencing ALEs may promote spinal facilitation, reflected by impaired inhibition during conditioned pain modulation of the nociceptive flexion reflex (CPM-NFR). Given that CPM-Pain remains intact, supraspinal inhibitory circuits could mitigate the enhanced spinal nociception so that hyperalgesia does not occur.

hyperalgesia does not subside, but is instead kept suppressed by endogenous inhibitory mechanisms (eg, endogenous opioids).<sup>56</sup> Nonetheless, this “latent” spinal sensitization places the animal at risk for future chronic pain. Subsequent exposure to environmental stress is one triggering event that can unveil the latent spinal sensitization to cause chronic pain in rodents.<sup>30</sup>

Thus, the current study contributes to this emerging story and shows that ALE exposure, in otherwise healthy and pain-free individuals, may promote latent spinal sensitization in humans by promoting descending facilitation of spinal nociception, without concomitant hyperalgesia. Further, the lack of association between ALEs and pain inhibition could indicate that *pain* inhibitory mechanisms (eg, purely supraspinal circuitry) are intact to suppress the spinal sensitization in healthy, pain-free persons exposed to high levels of ALEs.

### ***Psychological Distress does not Fully Explain the Relationship between ALEs and Pronociceptive Mechanisms***

ALEs were associated with CPM-NFR even after controlling for several physiological (ie, BMI, MAP, sleep quality, general health) and psychosocial variables (ie, psychological distress, perceived stress). Consistent with a growing body of research,<sup>55,68</sup> psychological distress did not sufficiently account for the effects of ALEs during experimental pain tasks. Indeed, other studies have observed that exposure to stressful life events (ie, trauma) may lead to a cascade of long-lasting adverse physiological consequences, including epigenetic changes in immune dysregulation<sup>54</sup> and hyperresponsivity in the hypothalamic-pituitary-adrenal axis.<sup>59</sup> That is, there is growing support for the notion that exposure to traumatic or potentially traumatic events may lead to physiological changes that are not wholly explained by psychological impairment. The present study is consistent with this literature and suggests that ALEs may lead to a disruption of descending, cerebrospinal, inhibitory circuitry, an effect that is at least partially independent of psychological distress/stress.

### ***ALEs Appears to Confer Pain Risk in Native Americans and non-Hispanic Whites***

The absence of a significant interaction with race suggests that ALEs may confer a similar level of chronic pain risk for NAs and NHWs. In other words, racial/ethnic group differences between NAs and NHWs appear to neither promote nor protect from the pronociceptive phenotype associated with ALEs. Nonetheless, NAs do experience more ALEs than NHWs on average<sup>33</sup>; thus, the greater frequency of ALEs for NAs may still contribute to observed disparities in chronic pain prevalence between these groups.

### ***Strengths and Limitations***

Several strengths in the current study are noted. First, this study benefited from using statistically powerful analyses (multilevel modeling) on a large, diverse sample. Next, subjective and physiological CPM outcomes were recorded (pain ratings and NFR), which allowed the study to assess perceptual versus spinal processes. In addition, physiological and background data were collected for each subject, so that analyses were able to control for variables known to affect CPM, and variables that differed between racial/ethnic groups. However, this study faced limitations as well.

Future studies may benefit from using alternative measures of ALEs, as the LEC does not measure all aspects of ALE exposure (eg, symptom presence, severity, chronicity, or duration) or the age at which an ALE was experienced. The age at which an ALE occurs may have an effect on its impact, as changes in epigenetic expression— especially during periods of significant neurodevelopmental plasticity— may worsen the lasting pathophysiological consequences of ALEs<sup>3,18</sup>; this process is known as biological embedding. Also, the LEC does not directly ask about other specific stressful life events that may yield similar pathophysiological consequences (eg, parental incarceration, divorce, poverty). Thus, the range of ALEs may have been restricted due to our use of the LEC. Nonetheless, the LEC is similar to the format of the questionnaire that has been used to assess the impact of adverse childhood experiences.<sup>1,13,16</sup>

Furthermore, CPM was only completed by 253 of the 302 study participants in OK-SNAP, indicating a potential selection effect; however, very few group differences were observed between CPM completers and CPM non-completers thus tempering this concern (Table 1). It is also worthy to note that our NA participants were recruited mostly from northeastern Oklahoma. It is not clear if our results will generalize to NAs from other geographical regions. Finally, the sample was healthy and pain-free, limiting the generalizability of these findings. For instance, people with more ALEs are susceptible to health conditions that were excluded for in OK-SNAP,<sup>1,16,31</sup> such that participants included in the study may have been less prone to negative sequelae from ALEs than the general population. Thus, caution is warranted in generalizing these findings to chronic pain populations. However, longitudinal data are being collected for this sample to determine whether these variables predict chronic pain onset.

### ***Conclusions***

This study suggests ALEs impair descending inhibition of spinal nociception, and high ALE exposure may even promote descending facilitation. By contrast, inhibition of pain perception was not associated with ALE exposure. Consistent with other findings from OK-SNAP,<sup>24,55,57</sup> racial/ethnic group did not moderate these effects. These results have at least 3 important contributions: 1) they contribute to accumulating evidence that

adversity promotes a pain risk phenotype that involves sensitization of spinal nociception, 2) they provide preliminary first evidence that latent spinal sensitization, an animal model of pain vulnerability, can be observed in humans, and 3) they extend our understanding of pronociceptive mechanisms in NAs.

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