Conditioned Pain Modulation in Sexual Assault Survivors

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Abstract: Sexual assault (SA) is associated with an increased risk of chronic pain, but the mechanisms for this relationship are poorly understood. To explore whether disrupted descending inhibition is involved, this study used a conditioned pain modulation task to study the inhibition of pain and the nociceptive flexion reflex (NFR; a correlate of spinal nociception) in 32 pain-free SA survivors. This group was compared with 32 pain-free, trauma-exposed persons without SA and a group of 40 pain-free persons who reported no trauma exposure. Conditioned pain modulation was assessed from painful electric stimulations (test stimulus) delivered to the ankle before, during, and after participants submerged their hand in painful 10°C water (conditioning stimulus). Pain ratings and NFR were assessed in response to test stimuli. All groups demonstrated significant inhibition of pain during conditioned pain modulation. However, only the no trauma exposure group demonstrated significant inhibition of NFR. The persons without SA group showed no inhibition of NFR, whereas the SA group showed significant facilitation of the NFR. These findings suggest that trauma exposure may impair inhibitory cerebrospinal circuits, but that SA may specifically promote facilitation of spinal nociception.

Perspective: This study suggests that trauma exposure disrupts the cerebrospinal inhibition of spinal nociception, but that exposure to SA further promotes chronic pain risk by facilitating spinal nociception. This finding help may help to elucidate the pain risk mechanisms in trauma survivors.

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Key words: Conditioned pain modulation, sexual assault, nociceptive flexion reflex, trauma, pain.

Sexual assault (SA), defined as exposure to any non-consensual sexual act, occurs in 1 in 4 women and 1 in 100 men, with a new incident occurring every 98 seconds in the U.S. SA has been linked to many negative outcomes, including chronic pain. Indeed, many people with chronic pain report experiencing SA (7–91%), but only a minority of SA survivors report sustaining a physical injury during the SA. Thus, injuries from SA are not likely to be responsible for chronic pain risk. Laboratory studies suggest that SA may promote chronic pain by disrupting pain processing. For example, SA survivors are hyperalgesic and have greater temporal summation of pain (a marker of central sensitization) compared with nontraumatized controls. Moreover, our recent study found that SA survivors displayed general hyperalgesia and failed to inhibit spinal nociception (assessed by the nociceptive flexion reflex [NFR]) in response to pleasant stimuli during an emotional modulation task. Interestingly, the inhibition of pain perception by pleasant stimuli (relative to neutral stimuli) was intact during the task, but not enough to offset the observed hyperalgesia. Given that studies indicate a corticocortical circuit (eg, anterior insula, orbitofrontal cortex, subgenual cingulate cortex [sgCC]) mediates the emotional modulation of pain, whereas a cerebrospinal
inhibition was associated with a cerebrospinal circuit that included the primary somatosensory cortex, paracentral lobule, supplementary motor area (SMA), premotor cortex (PMC), ACC, PCC, PHG, PFC, thalamus, and connections with the pons, periaqueductal grey, and rostral ventromedial medulla. Thus, CPM could be used to assess endogenous inhibitory circuits in SA survivors.

In a recent prospective study of 286 healthy, pain-free participants, we found that deficits in CPM-related NFR inhibition, but not deficits in CPM-related pain inhibition, predicted future onset of chronic pain. This finding suggests a role of the CPM cerebrospinal circuit in chronic pain risk. Given this finding, the present study investigated whether currently pain-free participants with SA (n = 32) had deficits in CPM of pain and NFR. To control for general exposure to trauma, this group was compared with a pain-free group with a history of non-SA trauma (no-SA; n = 32), who were matched for age, sex, race, and mean number of non-SA traumas. These 2 groups were compared with a pain-free control group without a history of trauma exposure (no-TE; n = 40). It was predicted that SA survivors would be hyperalgesic and fail to inhibit NFR. However, given evidence from a prior study of emotional modulation of pain, it was unclear whether they would fail to inhibit pain.

**Methods**

**Study Participants**

Participants were recruited from the community as part of a larger study investigating risk factors for chronic pain in Native Americans and non-Hispanic whites. Exclusion criteria included 1) <18 years old, 2) any history of cardiovascular, neuroendocrine, musculoskeletal, neurological disorders, 3) history of or current chronic pain, 4) body mass index of >35, 5) recent use of antidepressant, anxiolytic, analgesic, stimulant, and antihypertensive medication, 6) current psychotic symptoms (assessed by the Psychosis Screening Questionnaire) or substance use problems, and/or 7) an inability to read/speak English. Healthy, pain-free subjects were recruited to determine if disrupted pain modulation occurs before the onset of chronic pain and to rule out that disease status explains any group differences.

Participants completed laboratory testing over the course of 2 days, with each session lasting 4 to 6 hours. During each day of testing, participants completed a variety of tasks (painful and nonpainful) with mandatory breaks in between each task to avoid/reduce any carry-over effects. The current study focuses on the results from the CPM task, which was administered toward the end of one of the testing days and lasted approximately 15 minutes.

Two hundred fifty-one participants enrolled in and attended the first testing session; however, 27 withdrew before or during CPM. Multilevel modeling (MLM) does not exclude cases listwise; therefore, participants who began CPM were still considered for the current study (n = 224). Of those, 32 participants reported a history of SA (28 female) on the Life Events Checklist (LEC; a
commonly used measure of potentially traumatic events described elsewhere in this article). Of the 191 participants without a history of SA, a sample of 32 (28 female) trauma-exposed persons were selected as a control group matched on age, race, sex, and mean number of non-SA traumas (no-SA group). This matching procedure was intended to minimize the confounding influence of any group differences owing to general trauma exposure, age, sex, and race. Finally, those participants who reported no trauma exposure (n = 40; 13 female) were selected as no-trauma controls (no-TE). This design allows us to examine the effect that SA has on endogenous pain inhibition while controlling for the general effect of trauma exposure. However, owing to demographic differences in base rates of trauma exposure in the population, the no-TE group was not matched on all variables (similar to control groups used in other studies of trauma exposure). Thus, analyses controlled for these variables. Table 1 presents participant characteristics by group. Note that some participants in the SA and no-SA groups also participated in our published study of the emotional modulation of pain and NFR in SA survivors.

This study was approved by the Institutional Review Boards of The University of Tulsa, the Cherokee Nation, and the Oklahoma City Area Indian Health Service. During the informed consent process, participants were provided a detailed overview of all procedures and informed they could withdraw at any time. All participants provided verbal and written informed consent before enrollment and were provided $100 honorarium for the completion of each testing day (or $10/hour of every hour of testing completed).

**Testing Apparatus**

Study procedures were controlled by a computer with dual monitors, analog-to-digital converter (USB-6212 BNC; National Instruments, Austin, Texas) and LabVIEW.

### Table 1. Participant characteristics by group

<table>
<thead>
<tr>
<th>CATEGORICAL VARIABLE</th>
<th>NO-TE (n = 40)</th>
<th>NO-SA (n = 32)</th>
<th>SA (n = 32)</th>
<th>INFERENTIAL STATISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>N = 13, 32.5%</td>
<td>N = 28, 87.5%</td>
<td>N = 28, 87.5%</td>
<td>χ² = 33.349, P &lt; .001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>22, 55.0%</td>
<td>10, 31.3%</td>
<td>10, 31.3%</td>
<td>χ² = 9.742, P = .045</td>
</tr>
<tr>
<td>NA</td>
<td>14, 35.0%</td>
<td>21, 65.6%</td>
<td>21, 65.6%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4, 10.0%</td>
<td>1, 3.1%</td>
<td>1, 3.1%</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 h/wk</td>
<td>8, 21.1%</td>
<td>14, 43.8%</td>
<td>7, 21.9%</td>
<td>χ² = 8.204, P = .004</td>
</tr>
<tr>
<td>&lt;40 h/wk</td>
<td>16, 42.1%</td>
<td>9, 28.1%</td>
<td>18, 56.3%</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>14, 36.8%</td>
<td>9, 28.1%</td>
<td>7, 21.9%</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>10.888</td>
<td>12.342</td>
<td>12.357</td>
<td>.043</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.679</td>
<td>26.523</td>
<td>25.560</td>
<td>1.534, P = .221</td>
</tr>
<tr>
<td>Non-SA trauma # (LEC, 0-17)</td>
<td>–</td>
<td>2.156</td>
<td>2.156</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Global psychological distress (SCL-90, 0-4)</td>
<td>.210</td>
<td>.312</td>
<td>.479</td>
<td>.295, .001, .139</td>
</tr>
<tr>
<td>Pain catastrophizing (PCS, 0-52)</td>
<td>7.975</td>
<td>7.119</td>
<td>11.531</td>
<td>2.125, .125, .040</td>
</tr>
<tr>
<td>State anxiety (STAI, 20-80)</td>
<td>32.700</td>
<td>31.813</td>
<td>35.344</td>
<td>1.980, .143, .038</td>
</tr>
<tr>
<td>Perceived stress (PSS, 0-40)</td>
<td>12.250</td>
<td>15.613</td>
<td>15.264</td>
<td>3.454, .035, .065</td>
</tr>
<tr>
<td>NFR threshold (0-50 mA)</td>
<td>16.913</td>
<td>15.867</td>
<td>18.594</td>
<td>.608, .547, .012</td>
</tr>
<tr>
<td>Three-stimulus threshold (0-50 mA)</td>
<td>12.650</td>
<td>12.625</td>
<td>14.750</td>
<td>1.134, .326, .022</td>
</tr>
<tr>
<td>Stimulus intensity (0-50 mA)</td>
<td>26.233</td>
<td>11.297</td>
<td>25.636</td>
<td>.333, .717, .007</td>
</tr>
<tr>
<td>Cold water pain intensity (0-100)</td>
<td>51.200</td>
<td>56.750</td>
<td>24.870</td>
<td>.293, .055, .012</td>
</tr>
</tbody>
</table>

Abbreviations: NHW, non-Hispanic white; NA, Native American; PCS, Pain Catastrophizing Scale; STAI, State-Trait Anxiety Inventory; PANAS, Positive and Negative Affect Schedule.

Notes:

1 This analysis was conducted with an independent samples t-test because the no-TE group reported no traumas (Cohen’s d reported for the effect size instead of partial eta squared). Comparisons report differences between groups at P < .05.

2 These comparison analyses were conducted post hoc owing to a marginal overall significant difference between groups.
software (National Instruments). Participants completed study procedures in an experimental room and used 1 monitor to complete electronic questionnaires and provide pain ratings, while a researcher located in an adjacent room monitored physiology via the second monitor. Study procedures were conducted in a sound-attenuated and electrically shielded room. Throughout testing, participants wore sound-attenuating headphones to listen to pre-recorded instructions and communicate with the experimenter. In addition to monitoring physiology, the researcher monitored the participant via a video camera for study procedure compliance.

Electric stimuli were delivered to the left ankle over the retromalleolar pathway of the sural nerve by a stimulator (Digitimer DS7A; Hertfordshire, UK) and a bipolar electrode (Nicolet, Model 8019-40400, Madison, Wisconsin). Each electric stimulation was delivered as a train of five 1-msec rectangular wave pulses at 250 Hz and was perceived as a single stimulus. The timing of the delivery of electric stimuli was computer controlled. For safety purposes, the maximum intensity of each electric stimulation intensity was set to 50 mA.

To assess the NFR electromyography (EMG), 2 active Ag-AgCl electrodes were applied over the left biceps femoris muscle (located approximately 10 cm superior to the popliteal fossa). The EMG signal was filtered (10–300 Hz) and amplified (×10,000) using a Grass Technologies (West Warwick, Rhode Island) Model 15LT amplifier (with AC Module 15A54). An electrode was placed over the lateral epicondyle of the femur to serve as a ground. The participant’s skin was cleaned with alcohol and exfoliated (NuPrep gel; Weaver and Company, Aurora, Colorado) to achieve impedances <$5 kΩ for EMG and stimulating electrode. Electrodes were filled with conductive gel (EC60, Grass Technologies), and EMG signals were sampled at 1000 Hz.

**Questionnaires**

Participants provided demographic information and health status via a custom-built questionnaire to assess background information and study inclusion/exclusion criteria. SA history was determined via the LEC.31 A person was placed in the SA group if they endorsed “happened to me” for either of 2 items assessing SA.31 The remaining 14 items on the LEC that were answered “happened to me” were summed to indicate the number of non-SA traumas (for matching purposes and determining the no-TE group).

Participants completed additional questionnaires to assess groups’ differences in psychological characteristics known to affect pain19,38 and to allow for these variables to be entered as covariates if needed. The Symptom Checklist-90-Revised (SCL-90-R) assesses various psychological symptoms.46 The Global Severity Index of the SCL-90-R was used to assess current overall psychological distress (higher scores indicate greater distress). The Pain Catastrophizing Scale assesses catastrophic cognitions (eg, rumination, magnification, helplessness) associated with pain (higher scores indicate greater catastrophizing) and was administered via traditional instructions.66 The State-Trait Anxiety Inventory assesses the severity of state anxiety (higher scores indicate greater anxiety)62. The Perceived Stress Scale (PSS) assesses psychological stress within the past month (higher scores indicate more perceived stress).12

**Determination of Electric Stimulus Intensity Used During CPM**

Suprathreshold electric stimulus intensity (in mA) was individually calibrated to each participant before CPM testing. Because NFR magnitudes were a dependent variable in the current study, it was important to ensure that NFRs were reliably evoked throughout CPM testing. We have previously shown that setting the stimulus intensity above both NFR threshold and 3-stimulus threshold achieves this goal, whereas only setting it above NFR threshold does not.69 Interestingly, stimuli above the NFR threshold and the 3-stimulus threshold do not evoke pain in all individuals. Thus, a third calibration procedure was used (the Pain30) if necessary to ensure that stimuli were experienced as at least mildly painful in all participants. As a result, stimulus intensity was set to the highest of 1.2 times the intensity of NFR threshold, 1.2 times the intensity of 3-stimulus threshold, and 1 times the Pain30 (if necessary). During all 3 procedures, participants rated their pain intensity in response to each electric stimulus on a computer-presented visual analog scale (VAS) that ranged from 0 (no pain sensation) to 100 (the most intense pain sensation imaginable).54,69

**NFR Threshold**

The NFR is a spinal mediated withdrawal reflex evoked by Aδ fiber activation, wherein the limb (eg, leg) withdraws from a noxious stimulus.53,54,56,59 Given that the reflex requires the activation of Aδ fibers but its reflex arc does not require supraspinal regions (it is observed in spinally transected individuals57,76), the NFR is used as a correlate of spinal nociception. Moreover, NFR can be modulated by descending input from supraspinal centers6,46 and human studies have shown that NFR is inhibited by CPM.6,10,32,46

The NFR threshold was assessed using a well-validated paradigm that involved 3 escalating—descending staircases of stimulations.53 During this procedure, an NFR was said to occur if the mean rectified biceps femoris EMG in the 90 to 150-msec poststimulus interval exceeded the mean rectified biceps femoris EMG activity during the 60-msec prestimulus baseline interval by ≥1.4 standard deviations of the -60 to 0 msec prestimulation baseline EMG activity.53 The first ascending staircase began at 0 mA and increased in 2-mA increments until a reflex was observed (peak). After the first reflex, the stimulus intensity decreased in 1-mA steps until the reflex was no longer observed (trough). The subsequent 2 ascending—descending staircases implemented 1-mA step increments until all 3 peak and troughs were obtained. To minimize predictability and reflex habituation, the interval between electric stimulations varied
randomly (8–12 sec). The NFR threshold was defined as the average stimulus intensity (mA) of the peaks and troughs of the last 2 ascending–descending staircases.

Pain30
In the event that stimuli at the NFR threshold did not elicit at least mild pain (determined by a rating of ≥30 on the VAS), the Pain30 task was implemented. If assessed, the computer started the stimulus intensity (mA) at the NFR threshold and increased the intensity in 2-mA increments until a VAS rating of ≥30 was obtained. Fourteen participants (35%) in the no-TE group, 12 (38%) in the no-SA group, and 6 (19%) in the SA group underwent Pain30 assessment ($\chi^2 = 3.19; P = .203$).

The 3-Stimulus Threshold
The 3-stimulus threshold assessed NFRs in response to a 3-stimulus series (ie, each stimulation consisted of 3 trains of electric stimuli), with an interval of .5 sec between each stimulation (stimulations = trains of five 1-msec pulses at 250 Hz). The first series began at 0 mA and then the series increased by 2 mA until an NFR was evoked by the third stimulation in the series. That intensity was designated as 3-stimulus threshold.

In addition to determining the suprathreshold stimulus intensity used during CPM, the NFR threshold and 3-stimulus threshold were also used to assess group differences in general pain/nociceptive sensitivity. Pain30 was not used because it was not obtained for all participants.

CPM
The CPM is a validated paradigm used to assess brain-to-spinal cord pain inhibitory circuitry (a human analog of the diffuse noxious inhibitory controls used with animals). In brief, this task involves the assessment of pain in response to a test stimulus before, during, and after a tonic CS delivered at a distal body site from the test stimulus. In healthy humans, the CS should inhibit pain evoked by the test stimuli. In the present study, the test stimuli were electrical stimulations delivered to the left ankle at a random interstimulus interval between 8 and 12 sec. The CS was a circulating cold-water bath (Thermo Fisher Scientific, Pittsburgh, Pennsylvania) maintained at a temperature of 10 ± .1°C.

The CPM task consisted of three 2-min phases: baseline (test stimuli delivered before cold water), conditioning (test stimuli delivered while the hand/arm is submerged in cold water), and post-test (test stimuli delivered after conditioning). A 2-min rest occurred between baseline and conditioning and a 5-min rest occurred between conditioning and the post-test. During conditioning, participants were instructed to submerge their right hand up to their forearm in the water and to keep their hand palm down with fingers spread. During each 2-min phase, 5 electric test stimuli were delivered after a 20-sec wait period. Participants provided pain ratings in response to the electric stimulations verbally and an experimenter, in an adjacent room, recorded the ratings. After the conditioning phase, participants completed the VAS intensity scale for the pain elicited by the cold water. Pain from the cold water was also used to assess group differences in general pain sensitivity.

Pain Ratings
During each CPM phase, participants verbally provided pain ratings using a numerical rating scale (NRS). The NRS ranged from 0 (no pain) to 100 (worst possible pain). Anchors in between 0 and 100 were 20 (mild pain), 40 (moderate pain), 60 (severe pain), and 80 (very severe pain).

NFR Magnitudes
NFR magnitudes were used to assess within-subject changes in spinal nociception. NFR magnitudes were calculated as a change from baseline in microvolts (NFR change = mean rectified EMG of 90 to 150 msec post-stimulation interval minus mean of rectified EMG from −60 to 0 msec prestimulation interval). Stimulation trials with NFR baselines of >3.0 μV were excluded from analyses owing to excessive muscle tension and/or noise in the recording (5.6% of trials were excluded).

Testing Procedures
Figure 2 presents the tasks on the CPM testing day. The other testing day consisted of tasks assessing temporal summation of heat, pain thresholds/tolerances for electric, ischemic, cold, heat, and pressure stimuli. Testing day order was counterbalanced across participants but stratified by race and sex. Before pain tasks on the first testing day, participants completed a demographics questionnaire, the LEC, PCS, and State–Trait Anxiety Inventory. Within the 10– and 20–min breaks (Fig 2), participants completed several questionnaires presented in a randomized order, including the SCL–90–R and the PSS.

Statistical Analyses
Group differences in background variables were assessed via 1–way analysis of variance for continuous variables (such as age) and $\chi^2$ analyses for nominal variables (such as race), using group membership (no–TE, no–SA, SA) as the independent variable.

Data were tested for normality and within–cell outliers were identified using Wilcox’s MAD–median approach and winsorized (if necessary). Primary outcomes (pain ratings, NFR magnitude) were analyzed via MLM (MIXED procedure, SPSS. 20.0, IBM, Armonk, New York). Analyses of electric pain and NFR had 15 rows of data per participant, corresponding with the 5 electric stimuli delivered during each of the 3 phases (baseline, conditioning, and post–test). Level 1 units were responses to electric stimulations (pain/NFR). Level 2 units were participants. All models included a random intercept to model level 2 variance in the dependent
variable. The MIXED procedure used in SPSS implements Satterthwaite estimation procedures, which produce noninteger denominator degrees of freedom (which were rounded for ease of reporting). These degrees of freedom vary between analyses. Primary independent variables within the MLMs were group (no—TE, no—SA, SA) and CPM phase (baseline, conditioning, posttest). Additionally, a continuous variable that coded for the sequence of the 5 stimulations delivered during each CPM phase was entered to model habituation/sensitization effects (ie, stimulus number). Dependent variables within the MLMs were electric pain ratings and NFR change. Fisher’s least significant difference was used to test significant F-tests during follow-up tests. Significance was set at \( \alpha = .05 \) (2-tailed). In the event that significant group differences were found for background/psychological variables that might influence pain/NFR, these were entered into MLMs as covariates to control for these variables.

Results

Background Variables and Missing Data

Descriptive and inferential statistics for group differences in background characteristics are reported in Table 1. Owing to an equipment issue, SCL-90 and PSS data for 1 participant from the SA group were lost. The SA and no—SA groups were successfully matched for sex, race, age, and mean number of non—SA traumas. However, the no—TE group was more likely to be male and non—Hispanic white. The 3 groups did not differ on age, employment status, body mass index, pain catastrophizing, or state anxiety. However, the SA group reported more psychological distress on the SCL-90 (all \( P < .03 \)) and more stress on the PSS (all \( P < .04 \)).

One person in the SA group had excessive muscle tension in the EMG during NFR recording (ie, baseline EMG of \( >3 \mu \text{V} \)); thus, this person was excluded from the NFR analysis.

General Pain Sensitivity

Groups did not differ on NFR threshold or 3–stimulus threshold. This finding suggests that trauma exposure and SA history do not affect the general (tonic) sensitivity of spinal neurons. This also explains why suprathreshold stimulus intensity used during CPM testing did not significantly differ between groups (Table 1).

Group differences in cold water pain (CS) were marginally significant (\( P = .055 \)). Given this, exploratory posthoc analyses were performed that found the SA group reported more pain in response to the cold water than the no—TE group (\( P = .018 \)), but other comparisons were nonsignificant (all \( P > .14 \)).

CPM of Pain and NFR

Given the group differences noted, global distress (Global Severity Index of the SCL-90), perceived stress (PSS), sex, cold water pain, and minority status were entered as covariates in the MLM models. Also, stimulus intensity was entered as a covariate into the model predicting pain ratings to account for the individually calibrated intensities used during the CPM procedure. To control for sex, men were contrast coded as \(-1\) and women were coded as \(1\). To control for race, non—Hispanic whites were coded as \(-1\) and all others were coded as \(1\). Continuous control variables were grand mean centered.

The results of multilevel models predicting pain ratings during CPM are reported in Table 2, and the means and standard errors of the mean for pain ratings by group and CPM phase are reported in Table 3. A
significant main effect of CPM phase for pain ratings indicated that pain in response to the electric stimuli was significantly decreased during the cold water (conditioning) relative to baseline and post phases (all $P < .001$; Fig 3). However, this effect did not differ by group as indicated by the nonsignificant Group $\times$ Phase interaction. The significant effect of stimulus number was associated with a positive regression slope ($B = .665$), suggesting that pain sensitized across the 5 stimulations within each CPM phase. Further, cold water pain was significantly related to electric pain ratings ($B = .317$), as was the suprathreshold stimulus intensity ($B = .424$). Thus, higher values on both variables were associated with greater electric pain.

The results of the multilevel models predicting NFRs during CPM are reported in Table 4, and the means and standard errors of the mean for NFRs by group and CPM phase are reported in Table 5. In contrast with pain, CPM of NFR did differ by group as indicated by the significant Group $\times$ CPM phase interaction (Fig 4). The no-TE group demonstrated a significant decrease in NFR magnitudes during the post phase, relative to the baseline and conditioning phases (all $P < .03$). This finding suggests inhibition of NFR after the cold water. The no-SA group showed no differences in NFR across the 3 phases (all $P > .20$), suggesting a lack of CPM inhibition. The SA group demonstrated a significant increase in NFR magnitudes during the conditioning phase, relative to the baseline and post phases (all $P < .001$), suggesting facilitation of NFR. The significant effect of stimulus number was associated with a negative regression slope.

### Table 3. Means and SEMs for pain ratings during the 3 phases of CPM.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>BASELINE M (SEM)</th>
<th>CONDITIONING M (SEM)</th>
<th>POST M (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-TE</td>
<td>39.853 (2.910)</td>
<td>34.092 (2.900)</td>
<td>39.340 (2.910)</td>
</tr>
<tr>
<td>No-SA</td>
<td>39.344 (2.941)</td>
<td>32.274 (2.927)</td>
<td>38.181 (2.939)</td>
</tr>
<tr>
<td>SA</td>
<td>36.885 (3.099)</td>
<td>31.429 (3.088)</td>
<td>38.775 (3.098)</td>
</tr>
</tbody>
</table>

Abbreviation: SEM, standard error of the mean.
Suggesting that NFRs habituated across the 5 stimulations within each CPM phase. Further, cold water pain was significantly related to NFRs ($B = -0.020$); thus, greater cold water pain was associated with smaller NFRs.

**Discussion**

Contrary to our hypothesis, there was weak evidence for hyperalgesia in the SA group. Electric pain during CPM, cold water pain, NFR threshold, and stimulus threshold were not significantly different across groups. Only exploratory mean comparisons found that the SA group reported greater cold water pain than the no-TE group. Moreover, all groups displayed intact CPM-related pain inhibition.

By contrast, CPM-related NFR inhibition was disrupted by trauma exposure. The no-SA group failed to show significant NFR inhibition and NFR was facilitated in the SA group. Only the no-TE group demonstrated significant NFR inhibition, but this was only observed during post-test (after offset of the CS). It is not clear why inhibition of the NFR was delayed relative to the inhibition of pain; however, it is noteworthy that other studies have reported difficulties observing NFR inhibition during the CS and delayed CPM inhibition of spinal reflexes have been noted elsewhere. One possible explanation could be our use of 10°C water as the CS. When Goffaux et al. used 6.5°C water, they found a

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### Table 4. Results of multilevel models for conditioned modulation of the NFR.

<table>
<thead>
<tr>
<th>Predictors of NFR during CPM</th>
<th>$df_{num}$</th>
<th>$df_{denom}$</th>
<th>$F$</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>143.692</td>
<td>269.887</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race</td>
<td>1</td>
<td>101.768</td>
<td>.177</td>
<td>.675</td>
</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>100.886</td>
<td>.32</td>
<td>.573</td>
</tr>
<tr>
<td>Global psych distress</td>
<td>1</td>
<td>100.908</td>
<td>1.435</td>
<td>.234</td>
</tr>
<tr>
<td>Perceived stress</td>
<td>1</td>
<td>100.971</td>
<td>1.093</td>
<td>.298</td>
</tr>
<tr>
<td>Cold water pain</td>
<td>1</td>
<td>101.481</td>
<td>12.432</td>
<td>.001</td>
</tr>
<tr>
<td>Stimulus number</td>
<td>1</td>
<td>1,319.956</td>
<td>63.717</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group</td>
<td>2</td>
<td>101.014</td>
<td>.452</td>
<td>.638</td>
</tr>
<tr>
<td>CPM phase</td>
<td>2</td>
<td>473.075</td>
<td>10.015</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group $\times$ Phase</td>
<td>4</td>
<td>489.621</td>
<td>4.651</td>
<td>.001</td>
</tr>
</tbody>
</table>

### Table 5. Means and SEMs for NFR magnitudes during the 3 phases of CPM.

<table>
<thead>
<tr>
<th>CPM Phase</th>
<th>Baseline M</th>
<th>Baseline SEM</th>
<th>Conditioning M</th>
<th>Conditioning SEM</th>
<th>After M</th>
<th>After SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-TE</td>
<td>2.267</td>
<td>.289</td>
<td>2.444</td>
<td>.290</td>
<td>1.896</td>
<td>.290</td>
</tr>
<tr>
<td>No-SA</td>
<td>2.439</td>
<td>.297</td>
<td>2.205</td>
<td>.300</td>
<td>2.207</td>
<td>.299</td>
</tr>
<tr>
<td>SA</td>
<td>2.336</td>
<td>.316</td>
<td>3.118</td>
<td>.317</td>
<td>2.301</td>
<td>.316</td>
</tr>
</tbody>
</table>

Abbreviation: SEM, standard error of the mean.
large NFR inhibition during the conditioning phase. This finding is consistent with studies showing that the magnitude of CPM-related inhibition is correlated with CS intensity.\textsuperscript{30} Despite this, our CS temperature cannot explain why SA participants showed NFR facilitation. Together, findings suggest that trauma exposure disrupts the descending inhibition of spinal nociception and that SA exposure may tip the balance toward facilitation. There are several potential implications of these findings.

First, Yarnitsky\textsuperscript{80} argues that a person’s pain modulation profile, which ranges along a continuum between antinociceptive and pronociceptive, determines the likelihood of chronic pain development. Following this logic, the SA group should be at a higher risk for pain than both the no—SA and no—TE groups because their cerebrospinal modulatory system is shifted to facilitation (ie, extreme pronociception). Ostensibly, the no—SA group is still at a higher risk than the no—TE group owing to the inability to engage cerebrospinal inhibition.

Second, our findings suggest a role of the CPM-related cerebrospinal circuit in trauma-related pain risk. To our knowledge, only 1 study has examined the differential circuits involved with CPM of pain versus the CPM of NFR. Piché et al\textsuperscript{46} found that CPM of pain involved the orbitofrontal cortex, PCC, ACC, sgCC, anterior insula, amygdala, PHG, and medial prefrontal cortex, whereas the CPM of NFR involved the primary somatosensory cortex, paracentral lobule, SMA, pre—SMA, ACC, PCC, PHG, PFC, thalamus, and connections with the brainstem descending modulation circuit (pons, periaqueductal grey medulla, rostral ventromedial medulla). Given their findings, our data suggest deficits in the primary somatosensory cortex, SMA, pre—SMA, thalamus, and/or the brainstem modulatory circuit are responsible for chronic pain risk after trauma (Fig 1).

Third, the SA and no-SA groups both experienced a disruption of NFR modulation, but only the SA group displayed facilitation. Currently, it is unclear whether this difference is qualitative or quantitative. We made efforts to match the SA and no—SA groups on important variables, including number of non—SA traumas. However, this methodology means the SA group experienced more traumas overall. It is possible then that trauma exposure exerts a cumulative (quantitative) effect on spinal nociception, pushing it toward pronociception/facilitation. Consistent with this finding, a recent study from our laboratory found that trauma exposure has a dose—response relationship with temporal summation of the NFR (a marker of spinal cord hyperexcitability),\textsuperscript{65} such that persons with more trauma exposure demonstrated greater summation (ie, spinal hyperexcitability).

By contrast, differences seen between the SA and no—SA groups could reflect qualitative differences brought on uniquely by SA. For example, studies have noted that SA confers a risk for negative sequelae above and beyond other types of trauma (ie, mugging, physical assault, etc).\textsuperscript{45} At this time, the mechanisms contributing to the unique risk from SA are unknown. However, the mechanisms may include 1) epigenetic changes to the serotonin transporter promoter region,\textsuperscript{8,62} which could affect serotonergic neurons of the brainstem modulation circuit, 2) structural changes in brain regions responsible for pain processing/modulation,\textsuperscript{41} and/or 3) changes in the hypothalamic—pituitary—adrenal axis and/or stress responsivity.\textsuperscript{73,81} Additional research is needed to resolve this issue.

Fourth, our findings provide additional evidence that NFR modulation dysfunction may be a unique response to trauma exposure. Our laboratory has developed a method to study emotional modulation of pain and NFR and have repeatedly shown that, in healthy participants, positive emotions inhibit pain/NFR and negative emotions enhance pain/NFR.\textsuperscript{50–52,68} Recently, we found that SA was associated with an inability to inhibit NFR during positive emotions, even though pain perception was inhibited.\textsuperscript{32} This finding is similar to the current results, indicating that CPM inhibited pain, but not NFR, in SA and no-SA participants. Interestingly, we have found that persons with major depressive disorder,\textsuperscript{68} sleep disturbance,\textsuperscript{14} and fibromyalgia\textsuperscript{52} show a disruption of emotional modulation of pain, but not a disruption of emotional modulation of NFR. Given that major depressive disorder, sleep disturbance, fibromyalgia, and trauma exposure are all risk factors for chronic pain,\textsuperscript{1,4,5,11,21} then together these findings suggest that a disruption of NFR modulation (but not pain modulation) could be a unique pain risk factor for trauma survivors.

Finally, these findings may have treatment implications if SA and no-SA groups ultimately develop pain. As Yarnitsky\textsuperscript{80} notes, a decreased capacity to engage CPM inhibition implies a problem with serotonin and/or norepinephrine neurons involved with the brainstem descending modulation circuit. Thus, drugs that block the reuptake of serotonin and/or norepinephrine may rectify the dysfunctional NFR modulation. Alternatively, recent studies have shown that brief, cognitive—behavioral interventions can be used to train individuals to inhibit spinal neurons.\textsuperscript{7,17,18,36} These interventions alone or in combination could be helpful in stopping the transition to chronic pain or treating the pain once established in these individuals.

**Strengths and Limitations**

The present study assessed NFR so that inferences could be made about descending modulation of spinal
nociception in SA survivors and trauma-exposed persons. Further, matching was used to control for possible confounding between the SA and no—SA groups, and statistical controls were used to account for potential confounds between traumatized groups and the no—TE group. Additionally, multilevel models were used to improve statistical power. Finally, our sample consisted of ethnically diverse male and female participants, providing a better representation of SA and trauma survivors.

That said, our study is not without limitations. We assessed healthy, pain–free individuals to establish an association between SA and pain dysregulation before disease onset. Thus, it is unclear whether these findings will generalize to those with chronic pain. Further, owing to our limited sample size, we are unable to examine within—group differences that may be of interest (eg, sex/racial differences). Also, because of base rates in trauma exposure, we were unable to match the no—TE group with the other groups. In particular, the no—TE group was less likely to be female than the SA and no—SA group. Given evidence that females are more sensitive to experimental pain than males, this factor could have affected our results. However, no sex differences have been found for CPM—related NFR inhibition, despite evidence for sex differences in CPM—related pain inhibition. Thus, our group differences in NFR modulation are not likely to have been confounded by sex distributions.

Additionally, we are not able to evaluate whether SA characteristics impacted our findings, because the severity, frequency, and length of time passed since the SA are not measured by the LEC. We also did not assess for post—traumatic stress disorder or other psychiatric diagnoses, so we are unable to determine if clinically significant distress impacted our results. Also, our procedure for matching SA and no—SA participants by age, sex, and race on a case—by—case method may have created dependencies between the samples that we were not able to account for within the statistical models. Finally, participants were provided an overview of the study before their enrollment; thus, it is possible that self—selection bias may limit the generalizability of our findings.

Conclusions

These findings suggest that SA survivors and persons exposed to non—SA traumas display intact CPM—related pain inhibition. However, NFR was facilitated in SA survivors by CPM, whereas no NFR modulation was observed in non—SA trauma—exposed participants. This finding implies that trauma exposure impairs cerebrospinal inhibitory circuits, whereas SA exposure shifts descending modulation toward facilitation. This may represent one pathway to chronic pain for trauma exposed persons, including those with SA histories.

Supplementary data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2019.02.012.

References


12 The Journal of Pain


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