Anxiety Sensitivity Does Not Enhance Pain Signaling at the Spinal Level

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Objectives: Anxiety sensitivity (AS) is the fear of anxiety-related sensations and its perceived harmful consequences. AS is associated with enhanced pain and worsened pain outcomes, suggesting it is a contributing factor in acute and chronic pain. However, the mechanisms that mediate the relationship between AS and pain are currently unknown. This study assessed the relationship between AS and 2 measures of spinal nociceptive processes (ie, nociceptive flexion reflex and temporal summation of nociceptive flexion reflex) and measures of subjective pain. This allowed us to determine whether AS engages descending cerebrospinal processes to facilitate pain signaling at spinal levels.

Methods: AS was assessed in healthy men and women using the Anxiety Sensitivity Index-Revised. Then pain processing was assessed from electric pain threshold, nociceptive flexion reflex threshold, temporal summation of pain, temporal summation of nociceptive flexion reflex, and McGill Pain Questionnaire sensory and affective pain ratings. Associations among variables were assessed using Winsorized correlations (a robust and statistically powerful analytic method).

Results: AS was positively associated with sensory pain ratings, affective pain ratings, and temporal summation of pain, but was unrelated to all other outcomes.

Discussion: Given that AS was not significantly associated with measures of spinal nociception, these results suggest that AS may exert its influence on pain processing at the supraspinal, rather than the spinal level.

Key Words: spinal cord, plasticity, RIII reflex, anxiety sensitivity, spinal nociception


Anxiety sensitivity (AS) is an individual difference variable associated with fear of anxiety-related sensations and the belief that these sensations lead to harmful consequences.1,2 For example, increased heart rate may be interpreted as an oncoming heart attack. This fearful interpretation can occur during painful sensations as well. Indeed, studies have found a positive link between AS and enhanced pain perception in healthy individuals5–8 and those with chronic pain.9–10 As a result, AS may promote pain and other pain-related outcomes.9,11–12

The mechanisms that mediate the relationship between AS and enhanced pain are currently unknown; however, it is plausible that descending cerebrospinal processes are engaged to augment nociception (pain signaling) at spinal levels. For example, previous evidence has shown that cognitive-emotional processes (eg, mood, expectations, anticipatory anxiety) can modulate the nociceptive flexion reflex (NFR).13–16 A physiological correlate of human spinal nociceptive processes.17 Therefore, if greater AS is associated with a lower NFR threshold (the stimulus intensity that elicits the reflex) the implication would be that AS activates descending modulation to facilitate pain signaling at the spinal level. To date, however, no published study has examined the relationship between AS and NFR threshold.

AS may also enhance pain by promoting central sensitization (ie, central nervous system hyperexcitability). One method used to study central sensitization in humans involves using a paradigm called temporal summation of pain (TS-pain).18 TS-pain is the gradual increase in pain ratings after the delivery of several brief, constant-intensity, noxious stimuli that have a short interstimulus interval (ISI ≤ 3 s).19,20 TS-pain is thought to reflect the hyperexcitability of nociceptive dorsal horn neurons in response to repetitive C-fiber activation (a process referred to as wind-up in animal models).19–22 At least 1 study has shown that AS is associated with enhanced TS-pain.23 However, there are potential problems with assessing spinal sensitization from pain report, because pain report can be biased or modulated by factors that do not modulate spinal nociception, thus causing pain report and spinal nociception to diverge. For example, several studies have now shown that pain catastrophizing (another cognitive-emotional process associated with enhanced pain) is correlated with pain report and TS-pain, but not measures of spinal nociception.24–28

Temporal summation of NFR (TS-NFR) is a physiological measure of spinal cord sensitization. Indeed, the magnitude of the NFR gradually increases in response to repetitive noxious stimulations,29 and is dependent on mechanisms involved with windup (ie, N-Methyl-D-aspartic acid receptors).30 Furthermore, TS-NFR has been studied in both healthy31,32 and chronic pain populations.33 And chronic pain populations exhibit enhanced TS-NFR relative to healthy no-pain controls. Given that NFR is a measure of spinal nociception that does not rely on self-report, then TS-NFR should overcome the potential report bias that could influence TS-pain. To our knowledge, no study has examined whether anxiety sensitivity is related to TS-NFR.

To determine whether AS is associated with spinal nociceptive processes, this study assessed AS, NFR threshold, and TS-NFR, as well as electrotactile pain threshold, McGill Pain Questionnaire-Short Form (MPQ-SF) ratings of
electrocutaneous stimuli, and TS-pain. We predicted that higher AS would be associated with enhanced pain and spinal nociception on these outcomes. Alternatively, AS may be associated with measures of pain experience (pain ratings, TS-pain) but not measures of spinal nociception (NFR threshold, TS-NFR), which would suggest that AS does not engage descending cerebrospinal modulation to facilitate pain signaling at the spinal level.

**MATERIALS AND METHODS**

This is a secondary analysis of data from a parent study that examined different parameters to elicit TS-NFR. That study found that a 3-stimulation series delivered at 2.0 Hz worked best to elicit TS-NFR; thus, for this study TS-NFR and TS-pain were assessed from stimuli using those parameters. The analyses and results presented in this study are novel and have not been published elsewhere, although parts have been presented in poster form.35

**Participants**

Participants were healthy individuals recruited from the local community and the University of Tulsa psychology subject pool. Participants were excluded from participation if they had neurological, cardiovascular, or circulatory problems; chronic pain; recent psychological trauma; use of over-the-counter pain medication within 24 hours, or prescription pain medication within 2 weeks of participation; use of antidepressant, anxiolytic, or antihypertension medications; body mass index of 35 or greater [because high adiposity makes it difficult to record electromyogram (EMG) for assessing the NFR]; and age below 18 years. Fifty-eight eligible participants completed the study. One participant was excluded from analyses because pain tolerance was reached before the NFR could be obtained. The remaining 57 included participants were approximately 21 years of age (SD = 2.8 y), had obtained an average of 14 years of education (SD = 1.4), and were more likely to be female (63%, n = 36), white/non-Hispanic (61%, n = 35), and employed fewer than 40 hours per week (54%, n = 31).

**Apparatus**

Data collection and stimulus/questionnaire presentation were controlled by a PC equipped with dual monitors, A/D board (PCI-PCI-6071E; National Instruments, Austin, TX) and LabVIEW software (National Instruments). Testing procedures were conducted in a sound-attenuated and electrically shielded room. Questionnaires were administered on a 17-inch flat-screen monitor, placed approximately 0.5 M away from the participant. Participant activities were monitored from an adjacent control room by video camera. An experimenter monitored physiological signals in real time using computer.

Participants wore sound-attenuating headphones through which they received prerecorded experiment instructions. Participants were informed that they could communicate with the experimenter through the microphone on the video camera. A Digitimer stimulator (DS7; Digitimer Ltd, Hertfordshire, England) produced the electrical stimulations that were delivered to the participant using a bipolar surface stimulating electrode (Nicolet, Madison, WI; 30 mm inter-electrode distance) placed on the left ankle at the retromalleolar pathway of the sural nerve. Maximum stimulus intensity was set at 50 mA.

The NFR was measured using the biceps femoris EMG recorded from 2 adjacent Ag-AgCl sensors placed 10 cm superior to the popliteal fossa. A ground sensor was affixed to the lateral epicondyle of the left femur. Before sensor application, the surface of the skin was cleaned with isopropyl alcohol and scrubbed using an exfoliant gel (Nuprep; Weaver and Company, Aurora, CO) to decrease skin impedance below 5 kΩ. Conductive gel (Grass Technologies, West Warwick, RI; EC60) was applied to the sensors and they were attached using self-adhesive collars. Biceps femoris EMG was sampled at 1000 Hz and amplified/filtered using Grass Technologies Model 15LT amplifier (with AC Modules 15A54 and DC Modules 15A12).

**Anxiety Sensitivity**

The Anxiety Sensitivity Index-Revised (ASI-R) was used to measure fear of anxiety-related symptoms that are associated with a belief that anxiety will result in a variety of harmful consequences. The ASI-R is a reliable and valid 36-item scale. Item responses were made on a 5-point Likert scale indicating level of agreement, ranging from “very little” (coded “0”) to “very much” (coded “4”). The ASI-R was administered before pain testing procedures. Higher scores reflect greater AS.

**Pain and Nociceptive Outcomes**

For NFR threshold, pain threshold, and TS-NFR procedures, electric stimuli were sent to the retromalleolar pathway of the sural nerve. Each electric stimulus consisted of a train of 5 rectangular wave pulses of 1 ms duration with an interpulse interval of 3 ms (250 Hz). For NFR threshold and pain threshold testing, a single train of 5 electric stimuli was presented, which was experienced as a single stimulus. For temporal summation testing, a series of 5 trains of 5 electric stimuli was presented, which were experienced as 5 discrete stimuli. However, only the first 3 stimuli in the series were used in temporal summation analyses given that results from the parent study found that NFR reached an asymptote after the third stimulus.34

**NFR Threshold Assessment**

The NFR is a spinally mediated withdrawal reflex elicited after the activation of nociceptive A-delta fibers. The reflex is assessed from the biceps femoris (hamstring) EMG. The reflex arc does not require input from supraspinal centers, although it can be modulated from descending cerebrospinal mechanisms. Prior research has shown that NFR threshold (the stimulus intensity that elicits the reflex) is highly correlated with pain threshold, but under some conditions pain perception and NFR can diverge. For these reasons, NFR is used as a measure of spinal nociception. NFR threshold was determined using 3 ascending-descending staircases of electric stimuli. During the first ascending-descending staircase, stimulation intensity began at 0 mA and increased in 2 mA steps until an NFR was obtained. NFR was defined as a mean biceps femoris EMG response in the 90 to 150 ms poststimulus interval that exceeded the mean biceps femoris EMG activity during the 60 ms prestimulus baseline interval by at least 1.4 standard deviations. By restricting NFR measurement to the 90 to 150 ms poststimulus interval, contamination from the non-nociceptive RII response that can occur before 90 ms and from startle and voluntary responses that can occur after 150 ms is avoided. Once an NFR was obtained, the stimulus intensity decreased in 1 mA steps until it was no longer detectable. The subsequent 2 ascending-descending staircases used 1 mA steps. Time between
electric stimulations varied randomly between 8 and 12 s to reduce predictability and habituation. NFR threshold was defined as the average stimulus intensity (mA) of the last 2 peaks and troughs during the ascending-descending series. Lower NFR thresholds indicate enhanced spinal nociception, because less intense stimuli will evoke the reflex.

Pain Threshold Assessment

Pain threshold assessment was similar to NFR threshold assessment and used 3 ascending-descending staircases of electric stimuli (8 to 12 s varying ISI). Pain intensity ratings in response to electrical stimuli were assessed using a numerical scale ranging from 0 to 100, such that 0 indicates “no sensation,” 50 indicates that the stimulus is “painful,” and 100 indicates the stimulus is “the most intense pain imaginable.” The pain intensity scale was presented after each stimulus during pain threshold testing. The first ascending-descending staircase started at 0 mA and increased in 4 mA steps until pain threshold was reached (defined as a rating of ≥ 50 on the pain scale). The stimulus intensity was then decreased in 2 mA steps until a stimulation was rated as ≤ 40 on the pain rating scale. Of note, for the first 12 study participants, the descending series were stopped once a rating of ≤ 25, rather than 40, was obtained, but to shorten the length of the assessment and decrease the stimulus burden on the participant, the criterion was changed to ratings of ≤ 40. The second and third ascending-descending staircases continued with 2 mA steps. Pain threshold was defined as the average intensity (mA) of the stimuli above and below a rating of 50 on the last 2 ascending and descending series. A lower pain threshold indicates enhanced pain processing.

MPQ-SF

The MPQ-SF is a reliable and valid measure of subjective pain experience using 11 sensory (eg, throbbing, shooting) and 4 affective (eg, sickening, fearful) pain descriptors on a scale from 0 (none) to 3 (severe). Participants completed the MPQ-SF after the electrocutaneous pain threshold test with instructions to rate their overall experience of the electric stimuli they just received. Sums of sensory and affective pain words were used to compute sensory and affective pain rating scores, respectively. Higher scores reflect greater pain.

TS-Pain and NFR

During temporal summation (TS) testing, a trial was defined as a series of 5 stimulations (Fig. 1). Participants received a total of 25 trials delivered in 5 blocks. Each block contained 5 trials of stimulations. Each of the 5 trials in a block was presented using a different ISI: 3.0-s ISI, 2.0-s ISI, 1.0-s ISI, 0.5-s ISI, and variable ISI. The order of ISIs was randomized within each block and across participants. After each stimulus trial, a set of 5 computer-presented pain intensity scales were administered (such as the one presented during pain threshold testing). Participants were instructed to rate pain intensity for each of the 5 stimulations in the trial individually and then to click a button to submit their answers before the next series was delivered. The interval between trials was at least 8 seconds, but varied based on the time taken for the participant to complete the ratings. Participants were offered short (1 to 2 min) breaks between blocks. This study found that TS-NFR was optimally evoked by 2.0 Hz trials (those with a 0.5-s ISI)36; thus, for this study only the 5 trials at this stimulus frequency were used in analyses. In addition, TS-NFR reached an asymptote by the third stimulus in the series; thus only responses to the first 3 stimuli were used in these analyses.

To assess TS-NFR, NFR magnitude (the size of the reflex) was calculated in response to each stimulus. Prior research has shown that NFR magnitude is positively correlated with pain ratings17,41 and can be modulated by cognitive-affective processes.15,42,43 Therefore, changes in NFR magnitude are used as to assess changes in spinal nociceptive processes. NFR magnitude was defined as the mean EMG (μV) in the 90 to 150 ms poststimulus interval minus the mean EMG (μV) in the 60 ms interval before the first stimulation in the series (baseline 1). The first baseline...
was chosen because other baselines were contaminated by muscle tension for some participants (Fig. 1). TS-NFR was defined as the NFR magnitude in response to stimulus 3 minus the NFR magnitude in response to stimulus 1 (ie, ΔμV), given that the NFR asymptoted after the third stimulation. 43 TS-pain was defined as the pain rating in response to stimulus 3 minus the pain rating in response to stimulus 1. Higher scores for TS-NFR and TS-NFR reflect enhanced pain processing.

Procedure

All procedures were approved by The University of Tulsa ethics review board. Verbal and written informed consent was obtained from all participants after study procedures were thoroughly described to them. Eligibility to participate was assessed using participants’ self-report of health status. Once eligibility was established, an experimenter trained the participants on how to use the computer-presented pain intensity scales. Next, the stimulating electrode and EMG recording sensors were applied. After sensor application, participants filled out the ASI-R.

The experimenter then described the 2 phases of the study. Phase 1 assessed subjective and physiological reactions to single electric stimulations (NFR threshold and pain threshold assessments) and generally lasted 20 to 30 minutes. The order in which participants received the NFR threshold and pain threshold testing was counterbalanced across participants and stratified by sex to maintain an equivalent sex distribution across testing order. Immediately after pain threshold testing, the MPQ-SF was administered with instructions to make retrospective ratings of the stimulations received during pain threshold testing. After the questionnaire was completed, a 5-minute rest break was provided and then phase 2 was initiated. Phase 2 assessed reactions to electric stimulations presented in a series (TS testing) and generally lasted 20 minutes. During TS testing, the stimulus intensity was set at the higher of the participant’s 2 thresholds: NFR threshold or pain threshold. To ensure relaxation of the biceps femoris muscle throughout pain testing, participants were seated in a comfortable reclining chair with leg rest extended, maintaining a resting knee angle of approximately 160 degrees. At the completion of the study, participants were thanked for their participation and received either research credit (for psychology subject pool participants) or a $25.00 honorarium (community participants).

Data Screening and Analysis

Fifty-seven participants’ data were available for analyses of NFR threshold, pain threshold, and MPQ-SF. However, 7 participants withdrew before TS testing was complete because they could not tolerate the electrical stimulations. The stimulation intensity setting during TS testing was higher for these 7 individuals because they had significantly higher NFR thresholds compared with participants who completed this phase of testing (M = 24.11 mA vs. 14.41 mA, P = 0.005). It is important to note that these 7 individuals did not differ from the other 50 in AS (P = 0.15).

In addition, visual inspection of TS data determined that NFRs were not reliably elicited (< 25% reflexes during the TS procedure) in 19 of the 50 completers, possibly because the stimulus intensity, which was based on individuals’ NFR and pain thresholds, was set too low (nonresponders = 9.68 mA vs. responders = 20.68 mA, P < 0.001). 44 To test this hypothesis, nonresponders were invited to participate in the study again. Ten agreed and were rerun through the entire study on a later date (within a span of 2 to 7 months after first testing). During retesting, a higher stimulation intensity was used—the higher of 150% of NFR threshold or 150% of pain threshold. Of the 10 who returned for testing, 7 had adequate NFR responses (> 25% NFRs occurring during TS trials), suggesting that the stimulus intensity was too low in the first testing session to reliably elicit the NFR. Therefore, there were 38 participants available for TS analyses in this study. There was not a significant difference in AS between those who were run through the experiment once and those who had to be retested (P = 0.29).

Preliminary data screening found that many of the variables had marked skewness, outliers, and/or heteroscedasticity. To overcome these problems, Winsorized correlations were used, as described by Wilcoxon. 45 This type of correlation is similar to trimming (removing data at the extremes), but instead of discarding extreme values it replaces extremely high values and extremely low values with less extreme values from the data. 46 In addition, a percentile bootstrap method was used for significance testing to allow for heteroscedasticity of the data. When data violate the traditional parametric assumptions, this robust Winsorized correlation is more statistically powerful than using a Pearson correlation. Six separate Winsorized correlations with bootstrapping were performed for each of the dependent variables (ie, NFR threshold, pain threshold, MPQ sensory pain ratings, MPQ affective pain ratings, TS-NFR, and TS-pain). As there were too few male participants in our sample and because we did not find a sex difference in ASI-R scores (P = 0.14), we chose not to include sex in our statistical models. All analyses were conducted using the R statistical package.

RESULTS

Means and SDs for pain outcomes and Winsorized correlations with the ASI-R are provided in Table 1. AS (M = 29.65, SD = 21.07) was not significantly correlated with NFR threshold, electocutaneous pain threshold, or TS-NFR, but it was positively correlated with MPQ sensory ratings, MPQ affective pain ratings, and TS-pain.

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<tr>
<th>TABLE 1. Means and SD of Pain Outcomes and Winsorized Correlations With Anxiety Sensitivity</th>
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<td>Pain Outcome</td>
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<tr>
<td>NFR threshold (mA)</td>
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<td>Pain threshold (mA)</td>
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<td>MPQ sensory ratings (0-33 units)</td>
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<td>TS-NFR (ΔμV)</td>
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<td>TS-Pain (Δ pain units)</td>
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*P < 0.05. †P < 0.01.

ASI-R indicates Anxiety Sensitivity Index-Revised; MPQ, McGill Pain Questionnaire-Short Form; NFR, nociceptive flexion reflex; TS-NFR, temporal summation of the nociceptive flexion reflex; TS-pain, temporal summation of pain.
DISCUSSION

This study examined the relationships between AS and pain reactions evoked by electrocutaneous stimuli. Results revealed AS was positively associated with MPQ-SF sensory and affective ratings and TS-pain. These findings are consistent with a meta-analytic review conducted by Ocañez et al., who examined the relationship between AS and pain outcomes across 41 different studies of clinical and experimental pain. The investigators found a reliable association between AS and pain experience in both clinical and nonclinical samples. Of particular note, Ocañez et al. found the relationship between AS and pain report (eg, MPQ sensory ratings, r = 0.32; MPQ affective ratings, r = 0.39) to be stronger than the relationship between AS and pain threshold/tolerance (r = −0.14). Given the smaller effect size of the latter relationship, this may explain why we failed to find an association between AS and electrocutaneous pain threshold. Indeed, AS seems to explain ≤ 3% of the variance in pain threshold, which is unlikely to be clinically meaningful.

This study extends prior research by demonstrating a lack of association between AS and measures of spinal nociception, that is, NFR threshold and TS-NFR. This suggests that AS does not enhance pain by engaging descending cerebrospinal mechanisms to facilitate pain signaling at spinal levels. Moreover, because TS-NFR was not positively related to AS, this suggests that the relationship between AS and pain is not mediated by spinal cord hyperexcitability (ie, central sensitization). Rather, AS seems to augment pain at the supraspinal level given the significant associations with TS-pain and MPQ-SF sensory and affective pain ratings. However, we cannot rule out that AS biases pain report instead of altering supraspinal pain signaling. To address this issue, future studies need to assess the relationship between AS and physiological correlates of supraspinal nociception (eg, cortical-evoked potentials, functional magnetic resonance imaging of the pain matrix).

Study Limitations

This study had a number of strengths including the measurement of physiological correlates of spinal nociception and the use of robust statistical methods to maximize power; however, there are a few limitations worth noting. First, this study involved young, healthy participants, and so it is not clear whether our results will generalize to other populations, including those with chronic pain. Therefore, future research should be conducted to examine this issue in pain populations and clinical populations who tend to have high anxiety sensitivity. Second, there were too few male participants in this study to adequately test whether the relationships with AS were different in men and women. However, it is noteworthy that we did not find a sex difference in AS in this sample. Third, 12% of the participants dropped out during TS testing, and we determined that these participants had a higher NFR threshold. Therefore, it is possible that this limits generalizability. However, it is noteworthy that the 7 dropouts did not differ from the other 50 completers in their level of AS. Fourth, NFRs were not reliably evoked in 19 participants during TS testing, potentially compromising power in the analysis of TS-NFR. However, confidence in our conclusions from these data is bolstered by the fact that (1) the relationship between AS and TS-pain was significant even with an attenuated sample and (2) the relationship between AS and NFR threshold was nonsignificant in the larger sample. Finally, it is important to point out that we cannot confirm the null hypothesis; therefore, to determine that AS does not engage descending cerebrospinal mechanisms to modulate spinal nociception, it will be important to replicate these findings in an independent and more diverse sample.

Summary

This study examined the relationship between AS and experimental measures of pain and spinal nociception. The results suggest that AS was positively associated with TS-pain and sensory and affective pain ratings, but not electrocutaneous pain threshold, NFR threshold, and TS-NFR. Therefore, AS may exert its pain modulatory effects at the supraspinal level, rather than at the spinal level.

REFERENCES


