Does pain catastrophizing contribute to threat-evoked amplification of pain and spinal nociception?

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Abstract

Unpredictable threat amplifies pain and spinal nociception (as measured by the nociceptive flexion reflex, NFR), but it is unknown whether pain catastrophizing mediates this threat-related amplification. To examine this, the present study experimentally reduced catastrophizing and examined the effect on threat-evoked pain/NFR facilitation. Healthy pain-free participants (N = 113) were randomly assigned to a brief 30-minute intervention designed to reduce catastrophic thoughts or a control intervention that involved education about pain neurobiology. Before the interventions, participants underwent a block of 8 pseudorandomly ordered periods of safe (no abdominal shock) and threat (abdominal shock possible) during which pain and NFR were evoked by electric stimulations to the ankle. After the safe/threat periods, participants rated pain intensity, pain unpleasantness, and situation-specific pain catastrophizing. The same test block was delivered after the intervention to examine changes in catastrophizing and threat-evoked pain/NFR facilitation. As expected, pain catastrophizing was reduced by the catastrophizing reduction intervention, relative to the control group. Furthermore, pain intensity, unpleasantness, and NFR magnitudes were higher during threat periods than safe. However, this threat-related pain/NFR amplification was not attenuated by the catastrophizing reduction intervention at the group level, although the intervention generally led to lower pain ratings (but not reduced NFR), regardless of the context. Nonetheless, bootstrapped mediation analyses found that reductions in catastrophizing mediated reductions in threat-related amplification of pain, but not NFR. This suggests that catastrophizing is partly responsible for threat-evoked pain amplification and provides further evidence that catastrophizing does not amplify pain at the spinal level.

Keywords: Pain catastrophizing, Threat, Anticipation, RIII reflex, Psychophysiology, Pain modulation

1. Introduction

Pain is part of an evolutionarily adaptive threat detection system that provides awareness about actual or potential tissue injury; however, pain is not directly proportional to the amount of noxious input or tissue damage. Indeed, cognitive-emotional factors can modulate pain and nociception. For example, when a noxious event is encountered in a context that is potentially threatening, pain is enhanced relatively to a safe nonthreatening context. Importantly, threat also enhances pain signaling (nociception). For example, neuroimaging evidence indicates that threat evoked by anticipation of a painful event modulates pain processing by activating cortical and subcortical nociceptive circuits, including the primary somatosensory cortex, anterior cingulate cortex, insula, thalamus, prefrontal cortex, periaqueductal grey, and hippocampal network. Threat also seems to engage descending brain-to-spinal cord mechanisms to modulate nociceptive input at the spinal level. For example, Willer et al. demonstrated that anticipation of a painful ankle shock could augment the nociceptive flexion reflex (NFR, a spinally mediated withdrawal reflex used as an indicator of spinal nociception). Threat-enhanced NFR was later replicated by Hubbard et al. who presented 2 cues. One cue signaled an impending abdominal shock (threat), whereas the other cue signaled an abdominal shock would not occur (safety). Painful ankle shocks to elicit NFR were delivered during both cues. The authors found that NFR was enhanced during the threat cue relative to the safety cue. What is currently unknown is whether pain catastrophizing mediates threat-enhanced pain and spinal nociception (ie, NFR). Pain catastrophizing, which involves rumination, magnification, and helplessness regarding pain, has been consistently shown to enhance pain. Threat contexts promote catastrophic thinking. Therefore, threatening contexts may promote catastrophic thoughts, which subsequently promote pain and spinal nociception. However, attempts to find a linkage between catastrophizing and NFR modulation have generally failed.

The strongest evidence for determining relationships among variables comes from experimental manipulation. Given that cognitive-behavioral techniques have been shown to successfully reduce catastrophizing and improve pain-related outcomes, the present study experimentally reduced pain catastrophizing using cognitive-behavioral techniques and examined the effect it had on threat-enhanced pain and NFR.
Hubbard et al.’s paradigm was used in the current study.27 Specifically, painful ankle shocks were delivered during 4 threat (abdominal shock possible) and 4 safe (no abdominal shock) periods to get a baseline of threat-enhanced pain and NFR. Then, participants were randomized to an intervention to reduce catastrophic thoughts or a control group that received pain education. Following these manipulations, the threat paradigm was administered again (posttest). It was hypothesized that (1) pain catastrophizing would be reduced in the experimental group, relative to the control group, (2) the threatening context would amplify pain and NFR, and (3) experimental reductions in pain catastrophizing would reduce threat-related pain/NFR amplification. If reducing/blocking catastrophizing reduces or eliminates threat-enhanced pain and nociception, this would provide experimental evidence that catastrophizing is involved in threat-enhanced pain and NFR. Bootstrapped mediation analyses were also conducted to formally test whether catastrophizing mediated the effects.

2. Materials and methods

2.1. Participants

Participants were 113 healthy pain-free individuals recruited from the University of Tulsa psychology subject pool, as well as non–subject pool participants from the Tulsa community. Subject pool participants received research credit and community participants received a $50 honorarium. Participants were excluded for the following self-reported conditions: (1) neurological, cardiovascular, or circulatory problems; (2) chronic pain; (3) recent psychological trauma; (4) use of over-the-counter pain medication within 24 hours, or prescription pain medication within 2 weeks of participation; (5) use of antidepressant, anxiolytic, or high blood pressure medications; (6) having a body mass index $\geq$35 (due to difficulty recording a nociceptive reflex because of high adiposity); and (7) being under the age of 18. Although they were not excluded from participation, participants who failed to catastrophize at baseline (ie, scored zero on the situation-specific Pain Catastrophizing Scale [PCS]) were excluded from analyses to eliminate problems with floor effects (the intervention would not be effective if the participant did not catastrophize). Participants were given information about the study procedures and were provided informed consent before testing. Participants were told that they were free to discontinue participation at any time during the study. All procedures were approved by The University of Tulsa Institutional Review Board and all participants provided informed consent.

2.2. Apparatus

Stimulus presentation, questionnaires, self-report ratings, and physiological data collection were controlled by a computer with dual monitor capacity, and A/D board (PCI-6071E; National Instruments, Austin, TX). LabVIEW software was used to control timing of the experimental protocol and all data reduction. One computer monitor was used by the experimenter to monitor physiological signals and experimental timing. The second monitor was used by the participant to complete electronic questionnaires, to make ratings of electric stimuli, and to present visual stimuli during the threat paradigm. Testing was completed in a sound attenuated and electrically shielded testing chamber and participants were monitored from an adjacent control room by a video camera connected to a flat panel monitor. Participants wore a pair of sound attenuating headphones that allowed them to hear the experimenter.

Electric stimuli to the sural nerve at the ankle to test pain and NFR was generated by a Digitimer stimulator (DS7A) and was delivered using a bipolar surface stimulating electrode (Nicolet; 30 mm interelectrode distance) attached to the left leg over the retromalleolar pathway of the sural nerve. Each ankle stimulus consisted of a train of five 1-millisecond pulses at 250 Hz, which is experienced as a single stimulus. Electric stimulations to the abdomen to evoke threat were delivered using a Grass Technologies stimulator (Model S88; West Warwick, RI), stimulus isolation unit (Model SIU8T), and constant current unit (Model CCU1). Each abdominal stimulus consisted of a train of seventy-five 1-millisecond pulses at 100 Hz, which was experienced as a long set of multiple pulses. The computer controlled the timing of all stimulations and the maximum stimulation intensity was set at 50 mA.

2.3. Electrode Application and Signal Acquisition

The NFR was assessed from biceps femoris electromyogram (EMG) recorded from 2 active Ag-AgCl electrodes that were placed 10 cm superior to the popliteal fossa. A ground electrode was placed over the lateral epicondyle of the femur. All electrodes were attached with self-adhesive collars after conductive gel (EC60; Grass Technologies) was applied. Before the ground and stimulating electrodes were applied, the skin was cleaned with alcohol and exfoliated using an abrasive paste (Nuprep; Weaver and Company, Aurora, CO) to reduce impedances below 5 kΩ. Electromyogram signals were sampled at 1000 Hz, amplified (×20,000) and filtered (10-300 Hz) online using a Grass Technologies Model 15LT amplifiers (with AC Module 15A54).

2.4. Questionnaires

2.4.1. Background variables

A custom-built demographic and health status questionnaire was used to obtain standard background information about the participants as well as information regarding health problems. It was administered immediately after informed consent. The questionnaire asked about potential relevant demographic information, such as gender, age, race, marital status, years of education, and employment status, as well as potential exclusionary criteria, such as cardiovascular problems, neurological problems, chronic pain, and medication use. This questionnaire was used to ensure participants met inclusion criteria for the study.

2.4.2. Pain catastrophizing

The PCS is a reliable and valid 13-item questionnaire that assesses catastrophic thinking associated with pain.57 Like our previous studies,46,47,58 the PCS was administered using modified instructions to assess situation-specific catastrophizing (“Thinking back to your experience during the electric stimulations, please indicate the degree to which you had these thoughts and feelings”). This allowed us to eliminate participants who did not catastrophize at baseline and to evaluate changes in pain catastrophizing that resulted from the cognitive-behavioral techniques. In addition, the PCS was administered before the study using the traditional instructions to assess trait catastrophizing. For both trait and situation-specific measures, all items were summed to achieve a total score that ranged from 0 to 52, with higher scores representing more catastrophic thinking.
2.4.3. Pain ratings

During threat-enhanced pain/NFR testing, participants completed a block of 8 alternating periods of safe (no abdominal shock) and threat (abdominal shock given) periods during which NFRs were evoked. After the block of stimuli, participants were asked to rate their pain intensity and pain unpleasantness in response to electrocutaneous stimulations delivered to the ankle using vertically oriented, computer-presented visual analog scales (VASs) that were scored 0 to 100. Anchors for pain intensity were “no pain sensation” and “the most intense pain sensation imaginable.” The anchors for pain unpleasantness were “not at all unpleasant” and “the most unpleasant imaginable.” To make ratings, participants moved an indicator upwards along the scales to indicate their ratings and submitted their answer by selecting a “submit” button. The scales returned to zero after participants submitted their ratings. Before the start of the experiment, participants were instructed how to use the computerized scales and how to discriminate between pain intensity and unpleasantness using standard instructions.41

2.5. Determination of electric stimulation intensities

Nociceptive flexion reflex threshold, 3-stimulation threshold, and abdominal shock “Pain 50” were first assessed to determine the intensities of electric stimulations used during testing. The intensity for testing pain/NFR was set at 120% NFR threshold or 120% 3-stimulation threshold, whichever was higher. The first electric stimulus rated ≥50 was used as the abdominal shock intensity.

2.5.1. Nociceptive flexion reflex threshold assessment

The NFR is a physiological correlate of spinal nociception53 and is clinically relevant because patients with chronic pain often show NFR facilitation suggesting spinal hyperexcitability.1,6,10,31 NFR threshold was assessed using a previously validated method21,44 that uses 3 ascending–descending staircases of electric stimulations. The first ascending–descending staircase started at 0 mA and increased in 2 mA steps until an NFR was detected. Nociceptive flexion reflex was defined as a mean biceps femoris EMG response in the 90- to 150-millisecond poststimulus interval that exceeded the mean biceps femoris EMG activity during the 60- to 100-millisecond prestimulus baseline interval by at least 1.4 SDs.44 Using the 90- to 150-millisecond poststimulus interval to define the NFR avoids contamination from non-nociceptive responses, such as startle and voluntary movements.12 After an NFR was obtained, the stimulus was decreased in 1 mA steps until an NFR was no longer detected. The second and third ascending–descending staircases used 1 mA steps. Nociceptive flexion reflex threshold was defined as the average stimulus intensity (mA) of the 2 peaks and 2 troughs of the last 2 ascending–descending staircases. The interval between electric stimulations varied randomly between 8 and 12 seconds to reduce predictability.

2.5.2. Three-stimulation threshold

A single ascending staircase was used to assess 3-stimulation threshold. The staircase started with a series of 3 electric stimuli (stimuli = five 1-millisecond pulses at 250 Hz) with a 0.5-second interstimulus set at 0 mA. The intensity of the stimulus series was increased by 1 mA until the third stimulus in the series evoked an NFR according to the definition used in NFR threshold testing. This procedure was used to ensure reliable reflexes during testing.58

2.5.3. Abdominal pain 50 assessment

Abdomen stimulations were delivered using a bipolar surface stimulating electrode placed over the left side of the lower abdomen. Pain 50 was assessed using 1 ascending series of electric stimuli (0.75-second duration, 100 Hz) with a varying interstimulus interval of 8 to 12 seconds. The first ascending series started at 0 mA and increased in 2 mA steps until Pain 50 was reached (rated ≥50 on VAS pain intensity scale). This stimulus level was used for abdominal shocks during the threat-enhanced pain/NFR paradigm.

2.6. Assessment of threat-enhanced pain/nociceptive flexion reflex

The threat paradigm was adapted from Hubbard et al.,27 and included 4 safe and 4 threat periods presented in a pseudorandom order that was the same for all participants (ie, the order was randomly determined with the limitation that a threat period always occurred first). Participants received abdomen shocks during 2 of the 4 threat periods. For threat periods that contained abdomen shocks, onset of abdomen stimulii varied randomly between 22 and 26 seconds after the onset of the threat period. Abdomen stimulation was used to elicit unpredictable moderately aversive threat. Participants were instructed that during the safe period, the computer would display the text “SAFE: No Abdominal Stimulation will be Given” and they would not receive abdominal stimulations while the text was displayed. In contrast, for the threat periods, participants were informed that when the text “DANGER: Abdominal Stimulation may be Given at Any Time” was displayed, they may or may not receive electric stimulation to the abdomen. Onset of test stimuli delivered to the ankle to assess pain and NFR during each threat/safe period occurred 9 to 21 seconds after every safe/threat period onset. A horizontal bar at the bottom of the screen filled from left to right as each second of the 30-second period ticked off (Fig. 1). To distinguish between the 2 types of electrical stimulations and to introduce the study, the participants were told: “This test will involve receiving electric stimulations to your ankle during 2 different situations. In one situation, you might receive a stimulation to your abdomen, and in the other situation you will not receive a stimulation to your abdomen.” To assess changes in spinal nociception due to threat and safe periods, NFR magnitudes were calculated in response to each ankle stimulus in standardized d units (d = [mean EMG in the 90–150-millisecond postshock interval – mean EMG response in the −60- to 0-millisecond preshock baseline]/average SD of the 2 EMG intervals).45 This response definition was selected because, relative to other scoring methods (eg, peak response, area under the curve), it correlates more strongly with subjective pain ratings and has better distributional properties.32,45

2.7. Experimental groups for manipulating catastrophizing

Participants were randomly assigned to one of 2 groups (stratified by sex) to manipulate pain catastrophizing: pain catastrophizing reduction or pain education.

2.7.1. Pain catastrophizing reduction group

This catastrophizing reduction intervention was an abbreviated version of existing interventions.35,60 Participants first received general education about pain and were provided a rationale for the manipulation. Specifically, participants were educated about pain pathways, gate control theory, and how multiple factors
(eg, endogenous endorphins) can influence pain experience by opening or closing the gate. Next, participants were educated about how negative thoughts or beliefs (eg, I can’t deal with this), negative memories (eg, this reminds me of a pain I’ve had in the past), or negative expectations (eg, this pain will get worse) might trigger the gate to open and cause more pain. By contrast, positive thoughts or beliefs (eg, there are things I can do to control or cope with this pain) or positive expectations (eg, no matter how bad it gets, I know I can cope with the pain) can trigger the gate to close leading to less pain. This introduced the notion of pain control statements, which were anticatastrophizing statements based on items from the PCS (see Supplemental Table 1 of Pain Control Statements, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A173). Participants were instructed to choose 3 statements from a list of 26. Participants then were guided through imaginal exposure practice exercises in which they were told to imagine going through the pain tests while repeating their pain control statements aloud. Finally, participants were told to say the pain control statements aloud during posttests and allow the painful events to occur without focusing on them.

2.7.2. Pain education group

The pain education group received information about pain and pain processing, emphasizing the neurobiology of pain. At no time were participants taught about pain modulation or the interface of thoughts, feelings, and pain. After completing the education, participants were reminded that the next phase of pain testing was identical to what occurred during baseline tests.

2.8. Procedure

All procedures were fully approved by the University of Tulsa Institutional Review Board and testing was administered in a single session. Participants who expressed interest in the study were telephoned and provided a brief study overview. If interested, they were given a cursory eligibility screen before a session was scheduled. On arrival at the laboratory, participants were provided a thorough description of the experimental procedures before informed consent document was obtained. Participants were provided the opportunity to ask questions regarding the study procedures and were informed that their behavior was monitored by a video camera to ensure compliance with study instructions. Next, a health status questionnaire and interview was administered to thoroughly assess inclusion/exclusion criteria. Then, participants were familiarized with the VAS rating scales and instrumented with electrodes. Participants were tested individually while sitting comfortably in a reclining chair with the foot rest extended (knee angle approximately 160˚). Participants were randomly assigned (stratified by sex) to the catastrophizing reduction group or a pain education group on entering the study.

Figure 1 depicts experimental procedures. Stimulation intensities were assessed from NFR threshold, 3-stimulation threshold, and abdominal stimulation Pain 50. Then, NFR reactivity was assessed from a block of 5 single stimulations and a block of 5 triple-stimulations (data presented elsewhere, Ref. 59), followed by the baseline threat testing block. Pain intensity, pain unpleasantness, and situation-specific catastrophizing were assessed immediately after the testing block (this was done to ensure that the catastrophizing reduction group could focus on their coping strategies during posttesting, without being interrupted to make pain ratings). After these tests, each group received their manipulation, followed by posttesting that was identical to the baseline tests, except that participants in the pain catastrophizing reduction group were told to use the coping strategies they learned and to repeat their pain control statements aloud. Once all testing was over, participants were debriefed and provided course credit (subject pool) or $50 honorarium (community).

2.9. Data analysis

To determine whether there were group differences in participant characteristics, 1-way analysis of variance (ANOVA) and chi-square analyses were used. For primary analyses of group
differences, linear mixed-model ANOVAs were used (MIXED procedure, SPSS 20). The threat paradigm data were analyzed with phase (baseline vs posttest) and trial type (safe vs threat) as within-subject variables and group (pain education vs catastrophizing reduction) as a between-subject variable. Stimulation number (the linear trend for the 8 ankle shocks within each testing block) was added as a continuous predictor to the model with NFR as the dependent variable to control for any habituation effects. The dependent variables were situation-specific pain catastrophizing, NFR magnitude, pain intensity ratings, and pain unpleasantness ratings. Significant F-tests were followed up using Fisher least significant difference (LSD) tests. In the event of a significant interaction that included the trial-type variable, the simple effect of trial type was examined; otherwise the simple effect of phase was examined. Significance was set at \( P < 0.05 \) (2-tailed).

Bootstrapped mediation analyses were conducted as follow-up tests to determine whether group-related changes in threat-enhanced pain/NFR were mediated by situation-specific pain catastrophizing. These analyses are based on regression models; therefore, the dependent variables (pain and NFR) and the mediator (situation-specific catastrophizing) had to be converted to change scores to capture the variance of the safe vs threat and baseline vs posttest differences. Specifically, the following generic formula was used to generate dependent variables for the mediation analyses: (Threat at posttest – Safe at posttest) – (Threat at baseline – Safe at baseline). This represents the potential decrease in threat-enhanced pain/NFR from baseline to posttest, i.e., lower scores represent a larger decrease in threat-enhanced pain or NFR from baseline to posttest than higher scores. The mediator was calculated as a change in situation-specific pain catastrophizing (posttest – baseline). The group variable was dummy coded as 0 = pain education, 1 = catastrophizing reduction.

2.9.1. Data screening before analyses

After determining participants who were eligible for analyses, participants’ data were excluded partially or completely from analyses for several reasons: (1) complete data were excluded for participants who scored zero on situation-specific pain catastrophizing at baseline (to eliminate floor effects), (2) complete data were excluded for participants who withdrew without completing posttests, and (3) individual NFR trials from a participant were eliminated due to movement that resulted in preshock biceps femoris EMG > 10 \( \mu \)V during NFR testing (resting EMG is typically 2-5 \( \mu \)V on average).

3. Results

3.1. Participant Dropouts, exclusions, and final sample

In total, 251 individuals contacted the laboratory, of which 34 were deemed ineligible by phone screen. Another 15 declined participation after receiving more information about the study and 72 failed to attend the scheduled laboratory session. Thus, 130 individuals were enrolled and provided informed consent. However, after the in-person health screening, 17 participants were deemed ineligible leaving 113 eligible participants who were randomized to the 2 groups (stratified by sex). Fifty-seven were randomized to pain education control group, but 5 quit during NFR threshold and 3-stimulation threshold tasks and were eliminated from analyses (3 found the stimulations too painful and 2 were unable to elicit an NFR). Furthermore, 1 did not complete posttests and 8 were excluded for scoring zero on baseline situation-specific catastrophizing; thus, data from 43 participants in the control group were available for analyses. Fifty-six participants were randomized to the catastrophizing reduction group. Of these, 4 quit during NFR threshold and 3-stimulation threshold tasks (3 found the stimulations too painful and 1 was unable to achieve an NFR). Furthermore, 1 participant was excluded for not following instructions (i.e., failed to say anticastrhopizing statements aloud during posttests) and 4 were excluded for scoring zero on baseline situation-specific pain catastrophizing. In total, 12 participants were excluded for scoring zero on baseline situation-specific catastrophizing. These participants did not differ from those included in the study on any background variable except trait catastrophizing and 3-stimulation threshold. Non-catastrophizers scored lower on trait catastrophizing and higher on 3-stimulation threshold (see Supplemental Table 2, online as Supplemental Digital Content at http://links.lww.com/PAIN/A173). Thus, data from 47 participants in the treatment group were available for analyses. Five trials in total were eliminated because of biceps femoris EMG baseline > 10 \( \mu \)V.

3.1.1. Sample characteristics

Table 1 presents group comparisons on demographic and other relevant characteristics. As can be seen, the only significant group difference was years of education; the catastrophizing reduction group had approximately 1 more year of education than the control group. Because groups did not differ on supra-threshold intensity (ankle stimulation intensity used during threat testing), any group differences noted in the findings of pain/NFR cannot be attributed to this potential confound.

3.2. Situation-specific pain catastrophizing

The main effect group was not significant (\( F_{1,90} = 1.90, P = 0.17 \)) (Fig. 2). But, the significant main effect of phase (\( F_{1,90} = 48.08, P < 0.001 \)) was qualified by the significant group \( \times \) phase interaction (\( F_{1,90} = 21.09, P < 0.001 \)). The simple effects of phase indicated that situation-specific catastrophizing was significantly reduced in the catastrophizing reduction group \( (P < 0.001) \), but not in the pain education group \( (P = 0.11) \). There were no significant group differences in baseline situation-specific catastrophizing scores \( (P = 0.38) \), suggesting the experimental manipulation significantly reduced situation-specific pain catastrophizing (hypothesis 1).

3.3. Pain ratings of ankle stimulations

For pain intensity (Fig. 3A), the significant main effects of group \( (F_{1,90} = 3.92, P = 0.05) \) and phase \( (F_{1,270} = 74.92, P < 0.001) \) were qualified by the significant group \( \times \) phase interaction \( (F_{1,269} = 23.87, P < 0.001) \). The simple effects of phase indicated both groups showed statistically significant reductions in pain intensity ratings from baseline to posttest \( (P < 0.05) \), regardless of trial type (safe vs threat). However, the simple effects of group indicated that pain intensity ratings were lower for the catastrophizing reduction group relative to the pain education group at posttest \( (P = 0.003) \), but not at baseline \( (P = 0.41) \). The main effect of trial type was also significant \( (F_{1,269} = 7.94, P = 0.005) \), indicating pain intensity was greater during threat periods relative to safe periods (hypothesis 2). However, there were no significant interactions with trial type: phase \( \times \) trial-type interaction \( (F_{1,269} = 0.01, P = 0.94) \), trial type \( \times \) group \( (F_{1,269} = 0.29, P = 0.59) \), phase \( \times \) trial type \( \times \) group \( (F_{1,269} = 0.01, P = 0.92) \). This suggests the experimental manipulation did not affect threat-amplified pain intensity (hypothesis 3).
For pain unpleasantness (Fig. 3B), the significant main effects of group ($F_{1,90} = 4.97, P = 0.03$) and phase ($F_{1,269} = 100.71, P < 0.001$) were qualified by the significant group $\times$ phase interaction ($F_{1,269} = 42.12, P < 0.001$). The simple effects of phase indicated both groups showed statistically significant reductions in pain unpleasantness ratings from baseline to posttest ($Ps < 0.05$), regardless of trial type (safe vs threat). However, the simple effects of group indicated pain unpleasantness ratings were lower during threat relative to the safe periods (hypothesis 2). However, there were no significant interactions with trial type: group $\times$ trial type ($F_{1,269} = 0.78$). The significant main effect of trial type ($F_{1,269} = 8.18, P = 0.01$) indicated that pain unpleasantness ratings were greater during threat relative to the safe periods (hypothesis 2). However, there were no significant interactions with trial type: phase $\times$ trial type ($F_{1,269} = 0.31, P = 0.58$), trial type $\times$ group ($F_{1,269} = 0.05, P = 0.83$), phase $\times$ trial type $\times$ group ($F_{1,269} = 0.04, P = 0.84$). This suggests the experimental manipulation did not affect threat-amplified pain unpleasantness (hypothesis 3).

### Table 1

Background characteristics of participants by group.

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<tr>
<th></th>
<th>Pain education group (n = 43)</th>
<th>Catastrophizing reduction group (n = 47)</th>
<th>$P$</th>
<th>$d$</th>
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<tbody>
<tr>
<td></td>
<td>N % or mean SD</td>
<td>N % or mean SD</td>
<td></td>
<td></td>
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<tr>
<td>Sex (% female)</td>
<td>18 58.1</td>
<td>22 41.9</td>
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<td>Ethnicity (% non-Hispanic)</td>
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<td>Race (% white)</td>
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<td>Marital status (% married)</td>
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<td>10 21.3</td>
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<td>Employment status (% employed)</td>
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<td>27 57.4</td>
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<tr>
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<td>29.23 12.26</td>
<td>0.58</td>
<td>0.12</td>
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<tr>
<td>Years of education</td>
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<td>15.31 2.33</td>
<td>0.02*</td>
<td>0.50</td>
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<td>Body mass index (kg/m$^2$)</td>
<td>24.45 4.59</td>
<td>24.79 4.82</td>
<td>0.73</td>
<td>0.07</td>
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<td>Systolic blood pressure (mm Hg)</td>
<td>120.62 14.29</td>
<td>117.86 13.14</td>
<td>0.34</td>
<td>0.20</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>78.19 10.46</td>
<td>75.73 9.86</td>
<td>0.26</td>
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<td>Pain Catastrophizing Scale-trait, PCS (0-52)</td>
<td>14.28 8.54</td>
<td>13.68 9.23</td>
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<td>Nociceptive flexion reflex threshold (mA)</td>
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<td>Suprathreshold stimulation (mA)</td>
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<td>26.23 12.13</td>
<td>0.33</td>
<td>0.21</td>
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</table>

* $P < 0.05$.

### 3.4. Nociceptive flexion reflex magnitude

The main effect of phase was significant ($F_{1,449} = 49.83, P < 0.001$), but this was qualified by a significant group $\times$ phase interaction ($F_{1,449} = 17.56, P < 0.001$) (Fig. 3C). The simple effects of phase indicated both groups showed statistically significant reductions in NFR magnitudes from baseline to posttest ($Ps < 0.05$), regardless of trial type (safe vs threat). However, the simple effects of group indicated that NFR magnitudes were surprisingly smaller for the pain education group relative to the catastrophizing reduction group at posttest ($P = 0.03$), but there were no group differences at baseline ($P = 0.84$). There was also a significant main effect of trial type ($F_{1,1011} = 45.70, P < 0.001$), indicating that NFR magnitudes were larger during threat periods relative to safe periods (hypothesis 2). However, there were no significant interactions with trial type: group $\times$ trial type ($F_{1,958} = 1.38, P = 0.24$), phase $\times$ trial type ($F_{1,1049} < 1, P = 0.99$), group $\times$ phase $\times$ trial type ($F_{1,1065} = 1.24, P = 0.27$). This suggests the experimental manipulation did not affect threat-amplified NFR (hypothesis 3). There was a significant main effect of stimulation number ($B = -0.02, P < 0.001$), indicating that NFR magnitudes habituated within each testing block. The main effect of group ($F_{1,90} = 1.60, P = 0.21$) was nonsignificant.

### 3.5. Bootstrapped mediation analyses

Table 2 presents these results. First, analyses examined whether pain catastrophizing mediated the effect of the group $\times$ phase $\times$ trial-type interaction on threat-enhanced pain and NFR (Table 2, top set of rows). This was performed, although the group $\times$ phase $\times$ trial-type interaction was nonsignificant because indirect effects can occur even in the absence of a total effect, meaning the catastrophizing might mediate the effects even when reductions in threat-enhanced pain/NFR are not observed in the group-level analyses. As can be seen, the bootstrapped test for the indirect effect provided evidence that change in pain catastrophizing mediated the effect on pain intensity and pain unpleasantness (ie, the bootstrapped confidence interval did not contain zero), but not NFR (the confidence interval contained zero). This indicates that pain catastrophizing does at least partially mediate the effect of the manipulation on threat-enhanced pain intensity and unpleasantness, but not threat-enhanced NFR. For example, the indirect effect of $-3.96$ for pain intensity ratings is interpreted to mean that persons in the catastrophizing reduction group showed a greater reduction of pain catastrophizing, which in turn was associated with a smaller enhancement of pain during threat compared to safe. A similar interpretation is true of pain unpleasantness.
4. Discussion

4.1. Efficacy of the pain catastrophizing manipulation

Situation-specific pain catastrophizing was significantly reduced by the catastrophizing reduction manipulation, relative to the control group. Importantly, there were no group differences in situation-specific pain catastrophizing at baseline, suggesting that any observed changes in situation-specific pain catastrophizing scores at posttest were not due to differences in initial levels. This suggests the catastrophizing manipulation was successful and underscores that even a brief 30-minute cognitive-behavioral intervention can lead to significant reductions in catastrophic thoughts in healthy individuals.

4.2. Threat-evoked amplification of pain and nociceptive flexion reflex

The current study used a threat paradigm adapted from Hubbard et al.\(^{27}\) and hypothesized that successful reductions in catastrophizing would decrease the amount of threat-enhanced pain and NFR (i.e., eliminate/reduce the difference in pain/NFR between threat and safe periods). Consistent with previous studies, anticipation of an unpredictable threat (the abdominal shock) enhanced pain and spinal nociception\(^{27,50,62}\), pain intensity, pain unpleasantness, and NFR were greater during threat periods relative to safe periods. But contrary to our hypothesis, the catastrophizing reduction manipulation did not significantly reduce threat-enhanced pain/NFR, although it did produce an overall reduction in pain intensity and unpleasantness (averaged across safe and threat periods; Fig. 3). Nonetheless, mediation analyses indicated there was a significant indirect effect through catastrophizing for changes in threat-amplified pain intensity and unpleasantness. These results have at least 4 implications. First, it suggests that the effect of catastrophizing on threat-amplified pain cannot be observed at the group level; rather, individual differences must be taken into account. Put another way, only those persons that benefitted the most from the catastrophizing reduction intervention showed any reduction in threat amplification of pain intensity and unpleasantness. When averaged at the group level, the effects washed out. That is why we were unable to observe the effects in the group (linear mixed-model ANOVA) analyses, but could see them in the mediation analyses.

Second, it suggests that catastrophizing can mediate the effects of threat-related amplification, but can also have a global...
effect on pain that is unrelated to threat amplification. Our data suggest that catastrophizing was amplifying pain at baseline (independent of threat) because pain was globally reduced after experimental reductions in catastrophizing (ie, the significant group \times phase interactions). In addition, threat produced amplification of pain and NFR (albeit a smaller amplification according to Fig. 3) that was unaffected by the intervention at the group level, yet catastrophizing partially mediated this threat effect as indicated by the mediation analyses.

Third, catastrophizing mediates changes in pain, but not NFR. This is consistent with numerous studies showing that pain catastrophizing is associated with pain facilitation (eg, Refs 23, 56, 57) and extends this work to demonstrate that experimental reductions in pain catastrophizing leads to a reduction in pain.59 Therefore, formal mediation analyses found that the reductions in pain intensity and unpleasantness were at least partially mediated by the reductions in pain catastrophizing. Given that changes in catastrophizing were experimentally manipulated, this provides evidence that pain catastrophizing can produce pain facilitation and that reducing catastrophizing can reverse this facilitation.

By contrast, the catastrophizing reduction manipulation did not reduce NFR. In fact, unexpectedly NFR magnitudes in the catastrophizing reduction group at posttest were larger than the pain education group. The control group was included because it was assumed that pain education would not have an effect on NFR; therefore, any observed changes at posttest would represent changes because of natural history (eg, habituation). If this assumption is true, then the group difference at posttest represents a reversal of habituation (or facilitation) of spinal nociception in the catastrophizing reduction group. While this sounds counterintuitive, there is some evidence to support this possibility. Specifically, several studies examining the effect of distraction (eg, mental arithmetic) on NFR magnitudes55 and NFR threshold19,14,43,44 have noted enhanced NFR during distraction (but see, Refs 2–4,64). Thus, instructions to use anticatastrophic coping statements may have produced a distraction-related facilitation of NFR. Although the reasons for this effect are unclear, it may stem from the fact that the NFR is under tonic descending inhibition that requires attentional resources to maintain.18,22,34 When resources are limited by a cognitively demanding task, then descending inhibition may be withdrawn causing a relative NFR facilitation. Future studies are needed to resolve this issue.

And finally, the fact that catastrophizing only mediated the effects on pain suggests that pain catastrophizing does not amplify pain by engaging descending brain-to-spinal cord circuits that modulates spinal nociception. This is consistent with previous correlational studies suggesting catastrophizing amplifies nociceptive processes at the supraspinal level, not the spinal level.19,24,32,47,59 Our ancillary correlational analyses also support this and provide additional evidence that situation-specific catastrophizing is a stronger predictor of pain outcomes than traditional (trait) catastrophizing.8,11,15

### 4.3. Study strengths and weaknesses

There are several strengths of the study. This is the first study to use an experimental design to examine whether catastrophizing is involved in threat-related amplification of pain and nociception. Second, this is one of the few studies to have studied the effects of catastrophizing by successfully experimentally manipulating it. Third, NFR was assessed as a physiological correlate of spinal nociception to determine whether modulatory effects could be observed at the spinal level. Fourth, a validated threat paradigm was used that is known to engage descending facilitation. Fifth, statistically powerful linear mixed models were used to analyze the group data. And finally, formal bootstrapped mediation analyses were used to assess whether pain catastrophizing mediated any changes in threat-enhanced pain and spinal nociception.

Despite these strengths, a few limitations should be noted. First, additional studies are needed to determine whether the results generalize to populations with clinical pain. Second, pain ratings were made retrospectively so that they would not interfere with the treatment group’s coping strategies at posttest; therefore, these outcomes may have been affected by recall bias. Nonetheless, results for pain ratings were in the expected direction and the results for NFR did not suffer from this potential confound. Third, the manipulation was face valid and could have also contributed to report bias (eg, demand characteristics or an unconscious desire to please the experimenter). Fourth, we did not assess whether the pain education group was spontaneously engaging in coping strategies during the posttest period. This might have helped explain why that group showed a decrease in NFR at posttest. And finally, we cannot rule out that attention/distraction may

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**Table 2**

Results of bootstrapped mediation analyses.

| Does catastrophizing mediate the effect of the intervention on threat-enhanced pain and NFR?: group \times phase \times trial type as the IV |
|---|---|---|---|---|
| **Dependent variables** | **Bootstrapped indirect effect** | **95% confidence interval** | **Conclusion** |
| Pain intensity ratings | -3.96 | -9.31 to -1.27 | Significant indirect effect |
| Pain unpleasantness ratings | -3.82 | -8.70 to -0.63 | Significant indirect effect |
| NFR magnitude | -0.03 | -0.10 to 0.04 | No indirect effect |

| Does catastrophizing mediate the effect of the intervention on global changes in pain and NFR?: group \times phase as the IV |
|---|---|---|---|---|
| **Dependent variables** | **Bootstrapped indirect effect** | **95% confidence interval** | **Conclusion** |
| Pain intensity ratings | -5.73 | -11.28 to -1.56 | Significant indirect effect |
| Pain unpleasantness ratings | -9.29 | -17.21 to -4.41 | Significant indirect effect |
| NFR magnitude | -0.06 | -0.14 to 0.01 | No indirect effect |

For the bootstrapped indirect effect analyses of the phase \times group \times trial type interaction, the variables used were as follows: (1) a change score was created for each pain-related DV (Threat at posttest − Safe at posttest) − (Threat at baseline − Safe at baseline) and used as the IV, (2) group was dummy coded (0 = pain education, 1 = catastrophizing reduction) and used as the independent variable, and (3) a change score was created for situation-specific pain catastrophizing (posttest − baseline) and used as the mediator. For the bootstrapped indirect effect analyses of the phase \times group interaction, the variables used were as follows: (1) a change score was created for each pain-related DV (posttest − baseline) and used as the IV, (2) group was dummy coded (0 = pain education, 1 = catastrophizing reduction) and used as the independent variable, and (3) a change score was created for situation-specific pain catastrophizing (posttest − baseline) and used as the mediator.

NFR, nociceptive flexion reflex.

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have contributed to some of the group differences because participants in the control group were not asked to say statements aloud. This decision was made because we were concerned that doing so would interfere with their ability to catastrophize given that catastrophizing involves cognitive-attentional resources. Future research is needed to parse out the independent effects of attention and catastrophizing, if such a study is possible. Despite these limitations, this study represents important progress toward determining the mechanisms of threat-enhanced pain and spinal nociception.

4.4. Summary

In sum, this study demonstrated that unpredictable threat enhances pain intensity, pain unpleasantness, and NFR; but these effects were not attenuated at the group level by experimental reductions of catastrophizing. Nonetheless, mediation analyses demonstrated that reductions in catastrophizing led to reductions in threat-enhanced pain intensity and unpleasantness, but not threat-enhanced NFR. Furthermore, pain intensity and unpleasantness (regardless of the context) were reduced in the treatment group, effects that were at least partially mediated by changes in catastrophizing. These results provide preliminary evidence that catastrophizing at least partially mediates the effects of threat-related amplification of pain and provide further evidence that catastrophizing does not modulate pain signaling at the spinal level.

Conflict of interest statement

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A137.

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References


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Terry EL, Thompson KA, Rhudy JL. Experimental reduction of pain catastrophizing modulates pain report but not spinal nociception as verified by mediation analyses. PAIN 2015;156:1477–86.


