Association of catastrophizing with interleukin-6 responses to acute pain

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Abstract

Catastrophizing exerts its deleterious effects on pain via multiple pathways, and some researchers have reported that high levels of catastrophizing are associated with enhanced physiological reactivity to painful stimulation. In this project, 42 generally healthy adults underwent a series of psychophysical pain testing procedures assessing responses to noxious mechanical, heat, and cold stimuli. Pain catastrophizing cognitions were assessed prior to and then immediately after the various pain induction procedures. Blood samples were taken at baseline and then at several time points from the end of the procedures to 1 h post-testing. Samples were assayed for serum levels of cortisol and interleukin-6 (IL-6). Both cortisol and IL-6 increased from baseline during the post-testing period (p’s < .05), with cortisol returning to baseline by 1 h post-testing and IL-6 remaining elevated. Pain catastrophizing, measured immediately after the pain procedures, was unrelated to cortisol reactivity, but was strongly related to IL-6 reactivity (p < .01), with higher levels of catastrophizing predicting greater IL-6 reactivity. In multivariate analyses, the relationship between catastrophizing and IL-6 reactivity was independent of pain ratings. Collectively, these findings suggest that cognitive and emotional responses during the experience of pain can shape pro-inflammatory immune system responses to noxious stimulation. This pathway may represent one important mechanism by which catastrophizing and other psychosocial factors shape the experience of both acute and chronic pain in a variety of settings.

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1. Introduction

Catastrophizing is a multidimensional, negatively-valenced, cognitive and affective response to pain that has emerged over the past decade as one of the most important determinants of short- and long-term pain-related outcomes [17,79,88,89]. Individuals who report high levels of catastrophizing show enhanced musculoskeletal tenderness and amplified pain sensitivity both
in non-patient samples [25,81] and in samples of patients with persistent pain [30,34,36,38,43,81]. In longitudinal studies, moreover, high catastrophizers also appear to be at elevated risk for the onset and persistence of pain syndromes such as low back pain [71] and post-surgical pain [67,85]. At present, the mechanisms by which catastrophizing exerts its deleterious effects have not been fully characterized, though cognitive-attentional processes, social interactions, and neural pain-modulatory systems have all been proposed as potential mediators of catastrophizing’s effects [17,89].

We recently reviewed the literature on catastrophizing’s influence on pain in the context of rheumatic disease [17], and suggested that catastrophizing might be directly or indirectly associated with inflammatory processes. For example, studies in rheumatoid arthritis (RA) have reported positive relationships between catastrophizing (or helplessness, one component of catastrophizing) and elevated indices of disease activity and inflammation [64–66,82,103]. Several of these investigations suggest directional relationships between catastrophizing and inflammation; for example, longitudinal RA studies have shown that high levels of catastrophizing prospectively predicted worsening erythrocyte sedimentation rates [1,27]. Catastrophizing is also associated with elevations in patient-related pain severity in rheumatologic samples [11,22,49–52], and may contribute to interactions between pain and the immune system, which have become a recent focus of basic pain research [96,97]. In general, the experience of pain appears to be associated with enhanced release of pro-inflammatory cytokines, which in turn sensitize the nervous system, promoting an amplification of pain transmission [4,5,13,44,84]. Indeed, pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and others show positive associations with pain severity among samples of RA, osteoarthritis, back pain, cardiac, and fibromyalgia patients [2,33,62,68, 86,94,95].

Collectively, these findings suggest that pain and inflammation are reciprocally linked, and hint that catastrophizing might be influential in shaping these interactions. To date, however, no studies have evaluated whether catastrophizing predicts aberrant inflammation-related responses to the experience of acute pain (in a controlled laboratory setting), although three published reports have documented the presence of cytokine reactivity to the application of calibrated noxious stimuli. Each of these studies noted significant increases in IL-6 following painful stimulation in healthy adults [58], patients with juvenile rheumatoid arthritis [80], and patients with persisting low back pain [32].

In the present project, we focus on assessing predictors of IL-6 and cortisol responses to acute painful stimulation in a sample of generally healthy adults. Both cortisol and IL-6 are stress-responsive parameters, and both are intimately involved in shaping short- and long-term inflammatory processes. We hypothesized that higher levels of pain-related catastrophizing would be associated with elevated IL-6 reactivity to pain, and potentially with blunted cortisol reactivity (i.e., since high pain tolerance is positively associated with cortisol reactivity to acute pain [16], and catastrophizing is associated with reduced tolerance for pain).

2. Materials and methods

2.1. Participants

Participants were 42 healthy adults, recruited from the community using posted advertisements. The sample was predominantly middle-aged (mean age = 43.8 ± 14.2 years old; range = 19–64), with a preponderance of men (n = 29, representing 69.0% of the sample). The majority indicated their race as “white” (n = 30, representing 71.4% of the sample), with the remainder being African-American (21.5%) or Asian (7.2%). Determination of eligibility for the study was made based on questionnaires and a medical history taken by a research nurse at a General Clinical Research Center (GCRC). Inclusion criteria for the study were age 18–64, and facility with the English language adequate to complete questionnaires; exclusion criteria were as follows: severe depression (BDI score > 34), history of myocardial infarction or other serious cardiovascular condition, peripheral neuropathy, pregnancy, Raynaud’s syndrome, vasculitis or peripheral vascular disease, use of immune-system-modifying medications (including steroids), current infection, history of any autoimmune disorder, history of any painful rheumatologic condition such as fibromyalgia, use of antidepressants, adrenergic receptor antagonists, or opioids, recent history of substance abuse or dependence, current or recent chronic pain syndrome.

2.2. Session protocol

All subjects provided verbal and written informed consent, and all procedures were approved by an Institutional Review Board. The setting for the study was a Clinical Research Center based within a university hospital. Participants arrived between 12:00 and 12:30; they had previously been requested to refrain from using over-the-counter medications or caffeine, smoking, or performing other than mild exercise prior to their arrival. After informed consent and screening for eligibility, participants completed questionnaires for approximately 10 min. Questionnaires included a medical history form, the Beck Depression Inventory, and the Pain Catastrophizing Scale [88], a well-validated, widely-used 14-item self-report measure of catastrophic thinking associated with pain [17].
Next, subjects were seated comfortably in a reclining chair and an indwelling catheter was inserted in the left forearm by a research nurse. After catheter placement, a 15-min period of rest was observed, following which 2 baseline blood samples (10 ml), separated by 5 min, were drawn. Subsequently, participants underwent the psychophysical stimulation procedure described below, after which additional (10 ml) blood samples were taken at several time points: immediately post-stimulation, 15 min post-stimulation, 30 min post-stimulation, and 60 min post-stimulation.

2.3. Psychophysical pain testing

Mechanical pain thresholds were assessed first using a digital pressure algometer (Somedic; Sollentuna, Sweden). As in previous studies [14,35,45], we selected several muscle/joint sites and bilaterally assessed pressure pain thresholds (PPT). PPTs were determined twice at each of the following sites on the right and left sides of the body in a randomized order: the belly of the trapezius muscle, the metacarpophalangeal joint of the thumb, and the quadriceps muscle, near the insertion of the quadriceps femoris tendon. At each site, mechanical pressure was applied using a 0.5-cm² probe covered with 1 mm polypropylene pressure-transducing material; pressure was increased at a steady rate of 30 kPa/s until the subject indicated that the pressure was “first perceived as painful.”

Next, contact heat stimuli were delivered using a Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). Thermal assessment included sampling of heat pain thresholds (HPTH) on the ventral forearm using an ascending method of limits paradigm with a rate of rise of .5°C/s [23]. Three trials of HPTH were performed first, followed by 4 trials of suprathreshold heat stimulation. In brief, 4 sequences of 10 rapid heat pulses were applied to the forearm, similar to prior studies [19,77]. Within each sequence, the procedure was as follows: from a 38°C baseline temperature, ten successive thermal pulses were delivered. The rate of rise and fall of the thermode temperature was 10°C/s, and target temperatures were delivered for approximately .5 s each. The thermode remained in a fixed position during administration of the 10 pulses, and was then re-positioned between sequences, with inter-sequence intervals of 2 min. Two different target temperatures (49°C, and 51°C) were utilized two times each in randomized order. Subjects verbally rated the painfulness of each thermal pulse on a 0–100 scale (0 = “no pain”, 100 = “most intense pain imaginable”) numeric rating scale.

Finally, responses to noxious cold were evaluated using a repeated cold pressor task (CPT), involving immersion of the right hand in a circulating cold water bath maintained at 4°C. The CPT is the most commonly used method of pain induction in the laboratory, and has demonstrated clinical relevance [6,24]. Several recent studies indicate that the CPT provokes increases in cortisol and norepinephrine, as well as producing increases in pro-inflammatory cytokine production [80]. In the present protocol, participants underwent a series of five cold pressor tasks, with the first 4 consisting of serial immersions of the right hand for 30 s, with 2 min between immersions. The 5th and final CPT involved an immersion of the right hand lasting until a participant reached pain tolerance (or a 3 min maximum). Participants rated the intensity of the cold pain on a 0–100 scale (“no pain” to “most intense pain imaginable”) every 15 s. Following the final CPT, participants continued to relax in the chair.

2.4. Catastrophizing

Catastrophizing during these pain experiences was measured using a 6-item scale derived from the Pain Catastrophizing Scale [88]; items query participants about feelings of helplessness, attention to pain, etc. during the laboratory pain tests that they have just undergone. This situation-specific measure of catastrophizing was assessed 3 times: immediately after the pressure pain testing, thermal pain testing, and cold pressor testing. Participants were asked to indicate the catastrophic thoughts they remembered experiencing during the pain procedures. We have previously validated this scale for use in laboratory settings [25]; this situation-specific assessment of catastrophizing immediately following a pain experience is in contrast to the standard assessment of catastrophizing with the PCS or other measures, wherein subjects are cued to reflect on prior pain experiences, and then report on the degree to which they habitually have catastrophized.

2.5. Physiological measures

Each blood sample was collected in a 10 ml tube and later transported to the GCRC Core Laboratory where it was centrifuged, aliquoted, and stored in a −80°C for later assay. Serum cortisol was assessed in duplicate using a radioimmunoassay (DSL Inc. Webstar, TX), with a lower-limit of detection of .11 μg/dl, a sensitivity of .11 μg/dl and an intra-assay coefficient of variation of <10%. A standard high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Minneapolis) was utilized to assess serum levels of IL-6 in duplicate. This assay has a lower limit of detection of .16 pg/ml, a sensitivity of .09 pg/ml, and an intra-assay coefficient of variation of <10%.

2.6. Data analysis

Changes in serum levels of cortisol and IL-6 were evaluated using repeated measures analysis of variance.
(ANOVA). Inter-relationships among study variables were evaluated using Pearson correlations, while relationships between catastrophizing and physiological reactivity to pain were assessed using partial correlations (i.e., controlling for baseline levels of cortisol or IL-6). In addition, a measure of area-under-the-curve (AUC) [26,31,70] was used to summarize overall levels of cortisol and IL-6. Finally, hierarchical linear regression was used to assess the unique association of catastrophizing with AUC summary indices of reactivity. Analyses were performed using SPSS.

3. Results

Participants generally arrived at the Johns Hopkins General Clinical Research Center between 12:00 and 12:30 PM. The mean time of the two baseline blood draws was 1:30 and 1:35, respectively. The mean time of the post-testing blood sampling was 2:35 PM (indicating that the psychophysical pain testing session lasted 1 h, on average), with the mean timing of subsequent blood samples at 2:49, 3:04, and 3:32.

Pressure pain thresholds were highest for the quadriceps (779.0 ± 318.6 kPa), followed by the trapezius (505.7 ± 229.0 kPa) and the thumb (395.3 ± 146.9 kPa). Heat pain thresholds, assessed on the volar forearm, were 44.9 ± 3.9 °C. Mean pain ratings for the suprathreshold thermal stimuli delivered to the arm were 56.0 ± 32.1 (on the 0–100 scale) for the 49 °C stimuli and 67.1 ± 29.1 (on the 0–100 scale) for the 51 °C stimuli. For the repeated cold pressor tests, mean cold pain ratings were 70.6 ± 24.1 (on the 0–100 scale), and the mean cold pain tolerance for the final CPT was 129.3 ± 63.5 s.

In terms of psychological functioning, BDI scores for the sample were quite low, with a mean of 2.5 ± 3.9. Scores on the Pain Catastrophizing Scale showed substantial individual variability, with a sample mean of 12.3 and a standard deviation of 10.3 (range: 0–50). Similarly, situation-specific catastrophizing scores had a mean of 10.2 ± 9.0. These scores were inter-correlated across all 3 assessment points (mean Pearson \( r = .57, p < .001 \)), and cronbach’s alpha for all 18 items was .89 indicating excellent internal consistency of these responses. Interestingly, and consistent with prior studies [18], situation-specific catastrophizing scores were not significantly correlated with either standard PCS scores (\( r = .02 \)) or BDI scores (\( r = .12 \)). Correlations of catastrophizing and BDI scores with pain responses are presented in Table 1; in general, situation-specific catastrophizing was associated with enhanced pain sensitivity while PCS and BDI scores were largely unrelated to pain responses.

As expected, and consistent with prior research, repeated measures ANOVAs indicated that cortisol \([F(4,164) = 6.5, p < .01] \) and IL-6 \([F(4,164) = 3.6, p = .02] \) serum levels changed significantly over the course of the testing session, though the patterns of change differed somewhat. From baseline levels, cortisol increased roughly 33% at 15-min post-testing, then returned to baseline levels by the 60-min post-testing point. IL-6 increases, on the other hand, peaked at approximately 65% above baseline at the 60-min post-testing time point; cortisol and IL-6 data are depicted in Fig. 1.

Interestingly, average pain ratings were not significantly correlated with either cortisol reactivity (\( r = .12 \) for the association of pain ratings with AUC for cortisol) or IL-6 reactivity (\( r = .08 \) for the association of pain ratings with AUC for IL-6). Partial correlations, controlling for baseline values of cortisol, indicated that situation-specific catastrophizing, PCS scores, and BDI scores were all unassociated with post-testing cortisol values (all \( p’s > .05 \)). However, partial correlations, controlling for baseline values of IL-6, revealed that situation-specific catastrophizing was positively related to IL-6 levels at 15 min post-testing (\( r = .34, p < .05 \), 30 min post-testing (\( r = .52, p < .01 \)), and 60 min post-testing (\( r = .49, p < .01 \)), as well as the AUC summary measure of IL-6 (\( r = .43, p < .01 \)). PCS scores were unrelated to IL-6 levels, and BDI scores showed marginal negative correlations with IL-6 levels immediately post-testing (\( r = -.26, p = .10 \)), and 15 min post-testing (\( r = -.28, p = .08 \)). Finally, situation-specific catastrophizing scores were examined as a unique predictor of IL-6 reactivity. The summary AUC measure of IL-6, with baseline IL-6 levels partialed out, was used as a dependent variable in the regression equation, and sex, average pain ratings during the testing session, PCS, and BDI scores were entered on the first steps, with situation-specific catastrophizing scores entered last as a predictor. Results are presented in Table 2; collectively, only situation-specific catastrophizing was associated with IL-6 reactivity, with higher levels of catastrophizing strongly predicting larger increases in IL-6 from baseline to the post-testing period. A similar analysis using the comparable AUC measure of cortisol revealed that none of these independent variables was a significant predictor of cortisol reactivity.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>SS Catastrophizing</th>
<th>PCS</th>
<th>BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat pain threshold</td>
<td>-.40**</td>
<td>.09</td>
<td>.07</td>
</tr>
<tr>
<td>Pressure pain threshold</td>
<td>-.25</td>
<td>.13</td>
<td>-.11</td>
</tr>
<tr>
<td>Heat pain ratings</td>
<td>-.35*</td>
<td>.29</td>
<td>.06</td>
</tr>
<tr>
<td>Cold pain ratings</td>
<td>-.48**</td>
<td>-.42</td>
<td>-.01</td>
</tr>
<tr>
<td>Cold pain tolerance</td>
<td>-.29</td>
<td>-.01</td>
<td>-.38*</td>
</tr>
</tbody>
</table>

SS, “situation-specific”; PCS, Pain Catastrophizing Scale; BDI, Beck depression Inventory. *\( p < .05 \); **\( p < .01 \).

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4. Discussion

In the present study, situation-specific catastrophizing was associated with reduced pain thresholds and with elevated pain intensity ratings for noxious heat and cold. In addition, the administration of noxious stimuli increased serum levels of cortisol and IL-6, as others have reported previously [3,58], and higher levels of catastrophizing were related to greater pain-related increases in IL-6. These are, to our knowledge, the first data to demonstrate a link between catastrophizing-related cognitive/emotional processes and inflammatory responses to acute painful stimulation, though catastrophizing has been associated with enhanced cardiovascular responses to noxious stimulation [20] and two functional MRI studies have reported that catastrophizing is associated with amplified activation of the pain neuromatrix [37,83].

These findings support earlier research indicating that, in non-clinical samples, task-specific measures of catastrophizing are significantly associated with enhanced responsiveness to experimentally-administered noxious stimuli [25], while trait measures of an individual’s typical degree of catastrophizing show less robust associations [16,18]. Similar findings have emerged recently in the depression literature, where day-to-day variability in “state” measures of depressed mood was associated with IL-6 levels while a “trait” measure of depressive symptomatology was not [78]. As we reported previously, these two measures of catastrophizing (i.e., situation-specific catastrophizing scores and PCS scores) are minimally correlated [18], indicating the distinctness of these constructs. Important differences between the two catastrophizing measures include the specificity and universality of the referent pain event (i.e., for the situation-specific measure, all subjects have just undergone identical pain induction procedures and are queried specifically in reference to that experience) and the immediacy of the recall. Moreover, consistent with cognitive theory and with prior research from our group, catastrophizing might represent a type of latent construct, requiring sufficient activation to exert its

Table 2
Results of hierarchical linear regression model predicting IL-6 reactivity to acute pain

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor variable</th>
<th>$R^2$ change</th>
<th>$F$ change</th>
<th>Standardized $\beta$</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sex</td>
<td>.03</td>
<td>0.8</td>
<td>-.14</td>
<td>.35</td>
</tr>
<tr>
<td></td>
<td>Mean pain rating</td>
<td></td>
<td></td>
<td>.07</td>
<td>.68</td>
</tr>
<tr>
<td>2</td>
<td>PCS</td>
<td>.02</td>
<td>0.4</td>
<td>-.07</td>
<td>.70</td>
</tr>
<tr>
<td></td>
<td>BDI</td>
<td></td>
<td></td>
<td>.09</td>
<td>.63</td>
</tr>
<tr>
<td>3</td>
<td>Situation-specific catastrophizing</td>
<td>.35</td>
<td>19.9</td>
<td>.75</td>
<td>.001</td>
</tr>
</tbody>
</table>

Note. IL-6 = interleukin-6, PCS = Pain Catastrophizing Scale; BDI = Beck Depression Inventory.

Fig. 1. Serum cortisol (panel A) and IL-6 (panel B) levels. Data points are group means; error bars represent SEM.

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effects [8]. In this study, the unfamiliar and potentially minimally-threatening laboratory pain procedures, while they do induce some situation-specific catastrophizing, may not be sufficient to activate the catastrophizing constructs assessed by the PCS (which assesses responses to prior situations involving clinical pain). For example, the consent procedures specify that there is minimal risk of tissue damage or actual harm, whereas previous pain experiences (e.g., acute injuries, etc.) might well involve such threats.

Promoting elevated inflammatory responses to the experience of acute pain might constitute an important mechanism by which catastrophizing shapes long-term pain-related outcomes in a number of chronic conditions. IL-6 induces muscle and joint hyperalgesia [7,15] and mediates the development of injury-induced hyperalgesia [90]. Moreover, IL-6 increases are associated with enhanced pain in healthy individuals exposed to the stresses of extended sleep deprivation [40]. Following surgery, IL-6 levels are associated with postoperative pain [33,56,57] and reduced functioning [61]. In samples of pain patients, IL-6 and inflammatory markers correlate with higher pain severity [12,53,62,68,86]. Collectively, these findings support the conclusions of recent reviews, that pro-inflammatory cytokines are likely to play a facilitatory role in the development and maintenance of persistent pain syndromes, including neuropathic pain [59,60,91,98,100,101]. In this study, catastrophizing predicted subsequent elevations in IL-6 well after the pain had ended; such prolonged facilitation of pro-inflammatory processes could play a role in shaping long-term pain outcomes across numerous pain states and disease processes. For example, catastrophizing has been implicated as an etiological or prognostic factor persistent pain syndromes such as postsurgical neuropathic pain [47,75], low back pain [71], and neck/shoulder pain [42,48,93].

The precise mechanism(s) by which catastrophizing might impact on inflammatory processes are far from clear, although the present findings do suggest that catastrophizing is not associated with blunted HPA-axis responses to pain. This result is consistent with other studies of cortisol responses to acute pain [16]. The behavioral effects of catastrophizing, including less use of active coping strategies [87,88] and greater vigilance to bodily sensations [69], may play a role in producing greater physiological/inflammatory pain responses. On the other hand, it seems reasonable to suppose that such processes would primarily impact the degree of pain experienced by the participants, and while catastrophizing was positively correlated with pain ratings, individual differences in those pain ratings were unassociated with cortisol or IL-6 reactivity. This lack of relationship between pain ratings and physiological reactivity to pain could potentially be explained by a threshold-level effect whereby once a certain level of pain is reached, physiological reactivity is likely to ensue, and that reactivity may be driven by factors other than the perceived intensity of pain. Although this possibility is speculative, two recent joint replacement studies offer indirect support. Among patients undergoing total knee replacement (who were not treated with anti-inflammatory medications), a twofold increase from baseline in plasma IL-6 levels was observed post-surgery, but those IL-6 levels were not correlated with the degree of reported knee pain [28]. Similarly, patients undergoing total hip replacement (who were not given anti-inflammatory medications) showed an increase of several orders of magnitude in IL-6 within cerebrospinal fluid, and those increases were also uncorrelated with the degree of postoperative pain [9].

Physiologically, elevated catastrophizing is related to amplified responses to acute painful stimulation in multiple regions within the pain neuromatrix. In fibromyalgia patients, higher catastrophizing was associated with enhanced hemodynamic responses to mildly painful pressure in brain areas such as dorsolateral prefrontal cortex, anterior cingulate cortex, and medial frontal cortex [37]. In addition, healthy subjects exposed to mildly painful electric stimulation showed a significant positive relationship between pain catastrophizing and pain responses in the prefrontal cortex, insula, and anterior cingulate cortex, though these relationships were altered during the experience of more intense pain [83]. Though speculative, one possible mediating pathway for catastrophizing’s effects on acute inflammatory responses is via a potential influence on the functioning of endogenous opioid systems. Both exogenous [10,63] and endogenous [73,74,102] opioids have been shown to exert inhibitory influences on cytokine-mediated pro-inflammatory responses to injury or stress. Interestingly, catastrophizing has been indirectly associated with reduced efficacy of opioid pain-modulatory systems in several studies. Pain catastrophizing has been associated with greater postoperative opioid analgesic requirements [46], implying that catastrophizing was correlated with reduced benefit of opioids per unit of medication administered. In addition, among a subgroup of healthy adults, higher levels of catastrophizing were correlated with reduced analgesic benefit (measured as a function of changes in pain threshold and tolerance) of IV pentazocine, a kappa-opioid agonist [29]. Finally, high levels of catastrophizing predict impairments in the functioning of opioid-mediated endogenous analgesic systems [39,99].

Some important limitations of this study will need to be addressed in future research. First, we applied multiple noxious stimuli during a rather lengthy psychophysical testing session and we are not able to identify which specific pain induction tasks were associated with cortisol and IL-6 reactivity. Indeed, without a
control condition, we cannot exclude the possibility that it was not the pain itself, but rather the stress of participating in the study, that drove the observed increases in IL-6. In addition, none of our pain models involved inflammatory pain (e.g., capsaicin), which might have yielded stronger associations between pain responses and IL-6 levels. Second, the sample was relatively small, limiting its power, and larger replication studies will be necessary before these findings can be considered definitive. Third, we assessed catastrophizing immediately after, not during, the experience of pain, leaving open the possibility that pain intensity affected participants’ immediate recall of catastrophizing, rather than catastrophizing amplifying pain intensity at the time of stimulation. Fourth, our measure of IL-6 reactivity showed no sign of decline at our final assessment point, 1 h after the end of painful stimulation. We are thus not able to determine the full time course of IL-6 reactivity to pain and it is possible that the increases in IL-6 continued, and/or that there were important individual differences in the recovery of IL-6 levels, that we were unable to measure. Finally, we do not have data addressing some of the potential mechanisms underlying the association between catastrophizing and IL-6 reactivity to pain. Additional methodologies, such as pharmacological challenges, will be necessary to determine the pathways through which catastrophizing exerts its influence.

In spite of these limitations, this study highlights the potential role of catastrophizing in modulating pain, supporting further research on the interface between psychological processes and central pain processing. We previously reported that catastrophizing is prospectively related to prolonged sensitization following resolution of acute pain [21], and other studies have also reported that catastrophizing predicts the future onset or worsening of chronic pain [41,55,71]. The amplification of inflammatory responses to acute stress may partly underlie catastrophizing’s enduring effects. Future studies of interventions designed to reduce catastrophizing and improve pain-related outcomes may benefit from the evaluation of pro-inflammatory cytokines such as IL-6 in assessing the potentially beneficial effects of reducing catastrophizing. Finally, if these findings are replicated, it is possible that reductions in catastrophizing could be shown to have broadly positive health effects, as IL-6 levels are prospectively associated with the development of conditions such as Type II diabetes [72,92] and cardiovascular disease [54,76].

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