Pain Catastrophizing and Salivary Cortisol Responses to Laboratory Pain Testing in Temporomandibular Disorder and Healthy Participants

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Abstract

Pain catastrophizing is an important variable in the context of acute and chronic pain. The neurophysiological correlates of pain catastrophizing, however, have not been rigorously evaluated. We examined the relationship between trait pain catastrophizing and morning salivary cortisol levels before and following a 45-minute laboratory pain testing session in healthy, pain-free (n=22) and temporomandibular disorder (TMD) participants (n=39). We also examined whether TMD patients evidenced generalized hyperalgesia and hypercortisolism. Pain catastrophizing was associated with a flattened morning salivary cortisol profile in the context of pain testing, irrespective of pain status. Cortisol profiles did not differ between healthy and TMD participants. TMD was associated with mechanical hyperalgesia only at the masseter. These data are the first to show an association between pain catastrophizing and elevated salivary cortisol profiles in the context of standardized experimental pain testing. These findings in both healthy individuals and those with chronic orofacial pain suggest that aberrant adrenocortical responses to pain may serve as a neurophysiologic pathway by which pain catastrophizing enhances vulnerability for development of chronic pain and maintains and/or exaggerates existing pain and associated morbidity.

Perspective—Neurophysiological mechanisms by which pain catastrophizing is related to acute and chronic pain recently have come under empirical study. Understanding of these mechanisms has the unique potential to shed light on key central nervous system factors that mediate catastrophizing-pain relations and therapeutic benefits associated with changes in catastrophizing and related cognitive processes.

Keywords

pain catastrophizing; pain threshold; temporomandibular disorders; HPA; pressure pain; thermal pain

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Temporomandibular joint disorders (TMD) affect an estimated 12% of the population[38], can promote pain and functional impairment, hinder quality of life56, and often are accompanied by depressive symptoms42,64,[65]. The onset and/or aggravation of TMD often covaries with the occurrence of environmental stressors, and is highly prevalent in other "stress-related" or "idopathic" somatic disorders, such as fibromyalgia[1,11]. Recent conceptualizations emphasize the multifactorial nature of TMD and jointly consider neurophysiological and psychosocial factors[11]. In the present study, we examined two such factors that we believe are implicated in the onset, maintenance and/or exacerbation of TMD: aberrant neuroendocrine responses to pain and pain-related catastrophizing.

There is growing consensus that altered basal and stress-induced HPA activity may exist in painful idiopathic conditions such as fibromyalgia3,4,[55] and irritable bowel syndrome[13]. Comparatively, there exists a relative dearth of research that has evaluated the integrity of the HPA axis in TMD, although some findings do suggest that TMD patients (relative to healthy controls) exhibit altered HPA dynamics. For instance, TMD patients exhibited a more robust cortisol response than healthy controls to psychological stress[30] and have been shown to exhibit 30–50% greater daytime plasma cortisol levels than matched healthy controls34. To our knowledge, no studies have systematically examined cortisol profiles in the context of standardized laboratory pain testing in individuals with TMD.

Pain catastrophizing has emerged as a critically important psychosocial construct in the context of acute and chronic pain[for reviews, see 17,31,45,52]. In TMD, catastrophizing has been linked to self-reported clinical pain, activity interference, negative mood, greater clinical exam findings and increased health care utilization56,[57]. Although there has been speculation concerning altered HPA axis responses to pain as a potential neurophysiological correlate of catastrophizing[17], whether this is the case has scantly been examined and has yielded conflicting results. In a recent study among healthy participants, little correlation was observed between pain catastrophizing and plasma cortisol responses to standardized laboratory pain testing[19]. However, Johansson et al.[29] reported that less diurnal cortisol variability among back pain patients scheduled for lumbar disc surgery was associated with the tendency to catastrophize about pain, suggesting compromised HPA integrity among certain individuals with persistent pain. We hypothesize that an exaggerated cortisol response to pain might be readily observed in a sample of TMD patients, for which pain is a particularly salient stimulus, versus a sample of healthy individuals, for which pain may be significantly less salient and disease processes have not yet yielded measureable influence on HPA function.

In the present study, TMD and healthy participants underwent standardized mechanical, heat and cold pain testing[19]. Our chief hypothesis was that associations between catastrophizing and cortisol responses to pain testing would be strongest for TMD versus healthy participants. We also examined whether TMD patients exhibited a more robust cortisol response to pain testing than healthy controls, irrespective of pain catastrophizing levels. Finally, there is evidence that TMD might be characterized by generalized hyperalgesia5,40,48,[62]. Hence, we examined whether TMD patients were characterized by lower pressure pain thresholds at masseter and "unaffected" extracranial sites (i.e., trapezius), lower heat pain thresholds, and greater suprathreshold cold pain ratings than healthy controls. Portions of these data were presented in poster/abstract form at the 2009 annual meeting of the American Pain Society[46].

Materials and Methods

Participants

We recruited TMD patients (n = 39) from a dental school-based, tertiary care, orofacial pain clinic and media advertisements for a larger prospective study concerning sleep disturbance and TMD pain and function. To be eligible, TMD patients had to receive a primary myofascial

TMD diagnosis based on published Research Diagnostic Criteria (RDC)[15]. All TMD diagnostics were conducted by an experienced dentist who has completed formal training in RDC procedures and undergoes periodic reliability calibration. Additional major eligibility criteria for TMD patients included: typical pain severity > 2 out of 10 and minimum symptom duration ≥ 6 months. We excluded patients reporting primary pain conditions or serious medical disorders other than TMD, current alcohol or drug abuse problems, and use of narcotics, antidepressants, anticonvulsants, or muscle relaxants within two weeks of study participation. Healthy controls ($n = 22$) were recruited from fliers posted at a major teaching hospital and medical school. Major eligibility criteria for healthy controls included an absence of: significant medical/psychiatric history within the prior 6 months, and lifetime history of Raynaud's disease, bipolar or psychotic disorder, recurrent major depression, substance abuse disorder, use of antidepressant medications within the past 6 months and history of chronic pain (i.e., lifetime history of persistent pain for ≥ 6 months).

Apparatus and Measures

Salivary Cortisol—Salivary samples were collected immediately prior to the start of pain testing, immediately following the pain testing procedures and 20-minutes following the pain procedures by having participants chew on a cotton role (Salivettes; Sarstedt, Numbrecht, Germany) for 30 seconds. Samples were centrifuged until a clear, low-viscosity supernatant emerged. Supernatants were then collected and stored at −30 °C until assay. Assays were performed in duplicate using a commercially available enzyme immunoassay (EIA) kit (DSL, Webster, TX, USA). This assay has a sensitivity of 0.11 μg/dl. The intra- and inter-assay coefficients of variation were < 10%.

Psychophysical Pain Testing

Pressure Pain Threshold (PPTh): A somedic algometer (Sollentuna, Sweden) was used to assess responses to mechanical pressure using a 0.502-cm^2 probe covered with 1-mm polypropylene material. Pressure was increased in a graded fashion at a rate of 30 kPa/sec until the participant reported pain threshold, defined as first felt pain. Once threshold was determined, application of pressure was terminated. PPTh was assessed bilaterally at masseter, forearm and trapezius muscle sites, over three trials, separated by at least 1 minute.

Heat Pain Threshold (HPTh): A computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel), a peltier-element-based stimulator with a 30-mm^2 surface area was used to deliver contact heat stimuli. HPTh was assessed three times on the left ventral forearm using an ascending limits method. The temperature increased from 32 ° C at baseline with a 0.5° C/sec rate of temperature rise19 until the participant pressed a button indicating when they first felt a painful sensation. The temperature of the thermode at the moment of the button press was recorded. Between trials, the positioning of the thermode was moved slightly up the arm to avoid overlapping the testing site. A 30-sec inter-stimulus interval was rigorously maintained. A maximum temperature of 52° C was used to prevent possible tissue damage. HPTh was defined as the average readings across all trials.

Cold Pain Ratings (CPR): Cold pressor pain was assessed by having the subjects immerse their hand up to the wrist in 4°C water for 45 seconds. This procedure alternated right and left hand submersions across four consecutive trials (two trial each hand) with a 2-minute inter-stimulus interval between each trial. The water temperature was maintained (±0.1 °C) by a refrigeration unit (Neslab, Portsmouth, NH), and was constantly circulated to prevent local warming around the submerged hand. The participant was prompted to rate their pain on a 0 (no pain at all) to100 (extreme pain) scale at 20 seconds post-submersion. They were instructed to remove their hand from the water following this brief procedure (or at any time if intolerable). Cold water immersion was repeated twice and ratings were averaged together.

Psychosocial Questionnaires

Pain Catastrophizing Scale (PCS)[51]: The PCS is a 13-item self-report questionnaire used to assess the degree to which individuals *typically* catastrophize about their pain. The questionnaire is considered a comprehensive assessment of the catastrophizing construct and includes items designed to tap magnification, helplessness and rumination dimensions. Participants are instructed to indicate the degree to which each item describes them in relation to their recalled pain experience on a 0 (not at all) to 4 (very much) scale. Possible scores range from 0 to 52 with higher scores indicating greater catastrophizing. The questionnaire has been validated in patient and non-patient samples and the factor structure appears to be invariant across participant sex and patient/non-patient status[7,43,44,51]. It is important to note that we employed the original version of the PCS, which assesses a trait-like tendency to catastrophize about pain.

Brief Symptom Inventory (BSI)[8]: The BSI is a 53-item self-report questionnaire that taps the participant's degree of psychological distress *over the past two weeks* across a number of symptoms domains. Responses are given on a 0 (not at all) to 3 (very much) scale. Possible scores range from 0 to 3 with higher scores indicating greater levels of distress. Here, we utilized the Depression subscale of the BSI (BSI-D) because of the well-known conceptual and empirical overlap between pain catastrophizing and depressive symptoms. It is important to note that results were virtually identical using the General Severity Index (GSI) of the BSI, which is a composite index of a participant's overall level of distress collapsed across each symptom dimension (we observed a zero-order correlation coefficient (r) of .78 between the GSI and BSI-D).

Procedures

All procedures were approved by the appropriate Institutional Review Boards and written informed consent was obtained for all study participants. All procedures took place in a university hospital-based General Clinical Research Center (GCRC). All participants were enrolled in a larger study aimed at characterizing associations between objective polysomnography (PSG) sleep indexes and pain sensitivity. The analyses of the present investigation are based on next-morning procedures following an adaptation evening of sleep in which all participants were allotted an uninterrupted 8-hr period for sleep that was structured around participants' habitual sleep-wake times, which were ascertained from a 2-week daily sleep diary. Forty minutes after final awakening participants were escorted to a nearby research laboratory for pain testing procedures. Participants were seated comfortably in an upright reclining chair and the procedures were explained to them. The pre-pain testing saliva sample was obtained just prior to pain testing (M = 52 minutes post-awakening). Mechanical and thermal testing procedures were conducted in a randomized order across participants. In all cases, the cold pain testing procedures were conducted last in the pain testing battery sequence. As in prior studies conducted by our laboratory[19], the pain testing procedures lasted approximately 45 minutes on average. Immediately and 20-min post-pain testing, saliva samples were again obtained. Cortisol typically follows a diurnal pattern, with an early morning peak approximately 40 minutes post-awakening, followed by a decline in levels throughout the day. Hence, our cortisol assessment occurred following the morning peak, and during the diurnal morning cortisol decline. Hence, effects of pain status and/or pain catastrophizing on cortisol patterns in the context of the experimental pain testing would appear as a flattened cortisol profile, or put otherwise, a diminished morning cortisol decline. Peak salivary free cortisol concentrations have been observed at approximately 30 minutes post-cold pressor pain[54], so we feel that our 20-minute post-pain testing battery recovery assessment was likely to capture peak pain-induced cortisol levels. The PCS and BSI were completed as part of larger packet of questionnaires provided upon study entry. Importantly, the tightly controlled inpatient environment afforded by the GCRC assured that all participants had not smoked,

eaten, ingested caffeinated or calorie-rich beverages or exercised prior to obtaining saliva samples. Hence, our salivary cortisol measurements were unlikely affected by such potential confounds[27,36].

Data Analysis

All statistical analyses were conducted using Statistical Analysis Software version 9.2 (SASv9.2). Differences in demographics, pain catastrophizing and depressive symptoms between TMD and healthy participants were examined using *t*-tests and χ^2 analyses as appropriate. We conducted a series of linear mixed-effects analyses using SAS PROC MIXED to characterize the cortisol response to pain testing in relation to PCS scores, pain status and their interaction. Within-subject nested variables included salivary cortisol values (μg/dl) at baseline and immediately and 20-minutes post-pain testing. These variables were represented by a three-level `Time' factor. Between-subjects variables included Pain Status (TMD, healthy), PCS (continuous), and 2- and 3-way interactions of Time, Pain Status and PCS. To determine whether TMD and/or pain catastrophizing were associated with cortisol responses to pain testing above and beyond depression symptoms, BSI-D scores were included as a between-subject variable in the model.

We subsequently examined whether TMD patients exhibited generalized hyperalgesia. Because we observed no laterality effects for PPTh at masseter or trapezius muscle sites, PPTh values at left and right sites were averaged to create a single PPTh index for the masseter and trapezius. To do so, 2 Pain Status (TMD, healthy) ANOVAs were conducted on PPTh, HPTh and cold pain ratings. Lastly, in light of prior established empirical relations between trait pain-related catastrophizing and laboratory pain testing[52], we examined partial correlations between pain catastrophizing and PPTh, HPTh and cold pain ratings (partialling variance attributable to BSI-D).

Results

Sample Demographic and Psychosocial Characteristics by Pain Status

Sample characteristics are provided in Table 1. TMD and healthy participants were closely matched on sex [$\chi^2(1) = 2.28$, $p = .13$], occupational status [$\chi^2(4) = 5.13$, $p = .27$], education [$\chi^2(3) = 1.89$, $p = .60$] and Body Mass Index [$t(59) < 1$]. TMD and healthy controls differed in marital status [$\chi^2(1) = 7.06$, $p < .01$], such that a greater percentage of TMD patients reported being married at the time of study participation. A greater percentage of TMD patients were Caucasian than healthy controls [$\chi^2(3) = 9.38$, $p < .05$], and those with TMD were significantly older than healthy controls, [$t(59) = 2.89$, $p < .01$]. None of these demographic factors were related significantly with PCS scores, cortisol, PPTh indexes, HPTh or cold pain ratings, so were not considered covariates in subsequent analyses.

Relative to healthy controls, participants with TMD reported higher PCS [$t(59) = 2.36$, $p < .05$] and BSI-D scores [$t(59) = 3.32$, $p < .01$]. It is important to note even though the TMD patients had greater depressive symptoms, mean BSI-D scores ($M = .23$, $SD = .31$) were well within the normal range based on normative data[8]. Again, BSI-D scores were utilized as a covariate in all subsequent analyses focused on pain catastrophizing given *a priori* conceptual and empirical links between these constructs.

Pain Status and Pain Catastrophizing Effects on Salivary Cortisol Responses to Pain Testing

Linear mixed-effects analyses yielded a significant main effect of Time [$F(2, 114) = 7.04$, $p < .001$], suggesting that all subjects (irrespective of pain status and variations in pain catastrophizing) exhibited ed a significant morning cortisol decline, even in the context of pain testing. Contrary to our hypothesis, a significant Pain Status $\times$ PCS $\times$ Time effect failed to

emerge [$F(2, 114) < 1$]. Investigation of 2-way interactions revealed a nonsignificant Pain Status × Time effect [$F(2, 114) < 1$], suggesting that cortisol responses to pain testing did not differ across Pain Status. However, a significant PCS × Time effect emerged [$F(2, 114) = 4.18$, $p = .018$]. Inspection of marginal means, displayed graphically in Figure 1, revealed that higher PCS scores (i.e., +1 SD) were associated with a blunted rate of cortisol decline from pre- to 20-minutes post-pain testing. A follow-up comparison confirmed this interpretation: a significant PCS × Time effect was noted for cortisol change from pre- to 20 minutes post-pain testing [$t(114) = 3.26$, $p < .05$]. These findings suggest that a tendency to catastrophize about pain is associated with flattened morning cortisol declines in the context of standardized laboratory pressure and thermal pain stimulation. It is noteworthy that no pain index was associated with cortisol (p's > .10), suggesting a dissociation between the markers of pain sensitivity assessed in the present study and adrenocortical responses to the pain testing.

Pain Status Effects on Pain Indexes

To examine whether TMD patients evidenced a pattern of generalized hyperalgesia, we conducted a series of ANOVAs with Pain Status (healthy, TMD) as the between-groups factor (see Table 2 for Means and SDs). We observed no group differences in PPTh at the trapezius site [$F(1, 58) < 1$] and HPTh [$F(1, 58) = 1.45$, $p = .23$]. We also failed to observe group differences on cold pain ratings, [$F(1, 58) < 1$]. However, TMD participants evidenced lower PPTh at the masseter site than healthy, pain-free participants [$F(1, 58) = 5.00$, $p < .05$]. These findings are not supportive of generalized hyperalgesia in the context of TMD. Not surprisingly, participants with TMD had lower pain thresholds at the site of pain, and the magnitude of this effect was quite robust ($d = .60$). Entering BSI-D scores as a covariate did not alter these findings.

Associations of Pain Catastrophizing and Pain Indices

To examine associations between PCS scores and pain indices, we computed partial correlation coefficients ($r_{partial}$) between PCS scores and pain indices with variance attributable to BSI-D scores partialled out. PCS scores were not significantly correlated with PPTh at masseter ($r_{partial} = .06$, $p = .64$), forearm ($r_{partial} = .05$, $p = .66$) or trapezius ($r_{partial} = −.08$, $p = .52$) sites, nor with cold pain ratings ($r_{partial} = .12$, $p = .37$). PCS scores also were not significantly correlated with HPTh, although the pattern of these data suggest that greater PCS scores were related to lower levels of HPTh ($r_{partial} = −.23$, $p = .07$).

Discussion

The principal aim of the present study was to examine whether pain catastrophizing is associated with aberrant adrenocortical responses to standardized pain testing, and among TMD patients in particular. We also were interested in whether TMD patients evidenced a stronger pattern of adrenocortical activity during painful stimulation than healthy controls and, lastly, whether TMD patients were characterized by generalized hyperalgesia. Although hypotheses were not fully supported, some noteworthy findings emerged.

Pain catastrophizing was not differentially associated with salivary cortisol profiles in the context of pain testing across TMD and healthy participants. However, we did observe that pain catastrophizing was associated with exaggerated cortisol responses to pain testing when collapsed across participant pain status. Put more appropriately in the context of the current study design, higher levels of catastrophizing were associated with a flattened or elevated morning cortisol profile in the context of acute pain. These are the first data to our knowledge that show a relationship between catastrophizing and salivary cortisol profiles in the context to standardized pain testing. These findings build on prior research suggesting that pain catastrophizing might yield maladaptive neurophysiological responses to painful experiences.

For instance, positive associations between *state* catastrophizing and interleukin-6 (IL-6) responses to highly similar laboratory-based quantitative sensory testing methods were recently noted[19]. Moreover, catastrophizing has been associated with amplified activation of neural regions involved in the processing and regulation of affective elements of pain[26,49].

It is noteworthy that relations between catastrophizing and cortisol responses to pain emerged in patients and non-patients alike. These data suggest that pain catastrophizing may serve as a risk factor for the development of persistent pain as well as aggravate and/or maintain existing chronic pain via HPA pathways. Aberrant HPA axis integrity has been associated with worse post-operative pain outcomes, including pain severity[23]. Moreover, hypo- and hypercortisolism have been associated with impaired inhibition of cellular pro-inflammatory cytokine proliferation[47]. This is particularly noteworthy in light of the fact that inflammation enhances central sensitization[12,39,53,63], thereby putatively increasing vulnerability for transition from acute injury to a state of chronic, unremitting pain, or exacerbation and maintenance of existing pain. With emerging (albeit limited) evidence that pain catastrophizing may be related *both* to exaggerated cortisol levels[29] *and* IL-6 activity[19], it becomes possible to speculate that catastrophizing may be associated with a heightened state of glucocorticoid resistance at the cellular level, carrying the potential to account for associations between catastrophizing and clinical pain as well as pain-related functional outcomes, including sleep disturbance, fatigue and reduced activity levels[21]. Although admittedly speculative, whether such processes play a role in shaping pain-related outcomes in association with catastrophizing represents a potentially intriguing direction for future research.

Pain catastrophizing was not associated with pressure and thermal pain threshold or cold pressor pain ratings, irrespective of pain status. Although it has been suggested that catastrophizing accounts for between 7 and 31% of variance in clinical pain[52], the literature has been rather mixed with respect to associations between pain catastrophizing and experimental pain sensitivity. It is important to keep in mind that all experiments must inform patients that they have control over any painful procedures through studies require informed consent. This likely limits the degree that catastrophizing processes ensue in a laboratory setting. Another intriguing idea is that trait-like assessments of pain catastrophizing may not capture responses to experimental pain testing as readily as state-like or situation-specific measures[14,16,28]. Indeed, trait measures of pain catastrophizing instruct participants to base responses on recall of prior painful experiences which may have little or nothing to do with the type, duration or intensity of laboratory pain. Situation-specific measures catastrophizing heed participants to base their responses on the laboratory pain experience. This approach has the benefit of standardizing the referent and minimizing potential influence of recall bias[37]. State assessments of catastrophizing appear to correlate more robustly with experimental pain than trait measures in healthy[14,16,18,19,28] and in some clinical samples (Campbell CM, Manuscript Under Review), and have been linked to exaggerated IL-6 in the context of acute pain stimulation[19].

It is noteworthy that we obtained a significant association between pain catastrophizing and cortisol responses to pain despite observing no association between catastrophizing and experimental pain sensitivity, or between any index of pain sensitivity and cortisol. It is possible that we failed to assess a crucial dimension of the catastrophizing-pain interface, such as pain-evoked distress, or hypervigilance to pain-related sensory and affective information[61]. For instance, it is possible that the sensory pain experience per se does not drive the catastrophizingcortisol association. Instead, it might be the affective constituent of pain that is exaggerated for pain catastrophizers[41], thereby triggering a more robust stress response. Unfortunately, our data cannot address this hypothesis. We also failed to observe an association between our indexes of pain sensitivity and cortisol. This finding is not inconsistent with prior research. For instance, a recent study reported correlations between "state" catastrophizing and

IL-6 responses to acute pain stimulation in the absence of an association between pain itself and IL-6[19]. Moreover, two studies[6,22] that examined IL-6 levels post-operatively failed to show an association between IL-6 levels and self-reported levels of post-operative pain; despite a disassociation between IL-6 and pain, these studies observed robust increases in IL-6 following surgery. It seems clear that an important area for future research is to isolate possible mechanisms by which pain and pain catastrophizing shape neurophysiological responses to pain. Thus far, it appears that a conceptual model linking catastrophizing to exaggerated neurophysiological responses to pain via increased pain per se is not a viable one.

TMD patients had lower pressure pain thresholds at the affected anatomical site than healthy controls. This finding enhances confidence that TMD diagnoses in the present study were accurate. However, evidence for generalized hyperalgesia among TMD participants was not observed, which is at odds with some prior investigations but consistent with others[48]. A plethora of factors appear to moderate pain sensitivity, and not taking them into consideration may have diminished our ability to detect generalized hyperalgesia in TMD patients, which is a highly heterogeneous disorder. One such genetic factor that highlights the heterogeneity in TMD are the single nucleotide polymorphisms (SNP) of the catechol-o-methyltransferase (COMT) genotype. A "pain sensitive" haplotype of this SNP enhances pain sensitivity[9,10,66, for exceptions, see 32,33] and has been identified as a likely genetic determinant of transition to TMD[8,10]. George and colleagues[24,25] have shown that a pain sensitive COMT diplotype moderate relations between catastrophizing and clinical pain report.

Recent work by our group suggests that sleep disorders are another important and prevalent moderator of alterations in generalized pain sensitivity in TMD[50]. We found that the diagnosis of primary insomnia (26% of TMD sample) was associated with generalized hyperalgesia in TMD, whereas sleep apnea diagnosis (28% of TMD sample) was associated with generalized hypoalgesia. We also found that reduced sleep efficiency is associated with impaired pain inhibitory function in TMD[20]. Failing to take into consideration potential moderating factors might have restricted our power to detect between-groups differences in responses to pain testing.

Some study limitations warrant mention. First, we conducted pain testing and obtained salivary samples for cortisol measurement in the morning during the diurnal cortisol decline. Although this may have limited our ability to detect pain status differences in salivary cortisol responses to pain testing, we nonetheless detected a significant association between pain catastrophizing and salivary cortisol responses. This may speak to the robust effect of catastrophizing on HPA responses to pain. Conversely, it is possible that the effect observed in the present investigation can be attributable to Type I error. Interestingly, a recent study revealed that absolute pre-stress *levels* of salivary cortisol are greater in the morning than in the afternoon or evening, where as salivary cortisol *responsiveness* to psychological stress does not appear to differ across morning and afternoon sessions[35]. Nonetheless, these findings require replication and extension.

Second, and not uncommonly, we did not include a no-pain control condition. Hence, associations between catastrophizing and salivary cortisol profiles might have had little to do with pain testing, instead representing an association with some "third" variable. However, it is well-recognized that cold pressor pain stimulates HPA response at both pituitary and adrenocortical levels[2]. Moreover, at present, there exists little empirical or theoretical reason to posit that catastrophizing would be associated with tonic exaggerations in HPA activity that are independent of pain exposure, particularly among healthy pain-free participants. Third, we do not have data that attest to the mechanism(s) by which pain catastrophizing is associated with adrenocortical activity. Even more problematic is that our cross-sectional approach does not allow for causal statements. The process of catastrophizing during pain exposure might enhance the subjective experience of pain, thereby affecting neurophysiological processes.

Conversely, exaggerated neurophysiological responses to pain might cause an individual to catastrophize. Potential "third" variable mediation of catastrophizing and exaggerated HPA responses to pain also cannot be ruled out. Lastly, we did not include measures of other negative pain cognitive process variables, such as fear of pain or pain anxiety. Hence, we can only tentatively speak to the specificity of the findings with respect to catastrophizing.

These limitations notwithstanding, these findings suggest an intriguing association between pain catastrophizing and exaggerated HPA activity in the context of acute standardized laboratory pain testing. These data point to a potential neurophysiological pathway by which catastrophizing may confer risk not only for the maintenance and/or exacerbation of existing TMD pain, but for the development or onset of persistent pain. Bridging these findings with those indicating exaggerated inflammation associated with catastrophizing[19] may yield novel insights into the processes by which pain catastrophizing shapes pain-related outcomes. Clinically, it has been well-documented that reductions in pain catastrophizing in the context of cognitive-behavioral therapy for TMD play a critical role in shaping immediate and longer-term outcomes[58–60]. It is a distinct possibility that cognitive-behavioral interventions not only affect cognitive processes that an individual brings to bear on painful encounters, but restores HPA function and crosstalk between neuroendocrine and immune pathways[4]. The study of the neurophysiological basis of pain catastrophizing is in its infancy, but these and other findings suggest that this promises to be an exciting and important area of investigation in the coming years.

Acknowledgments

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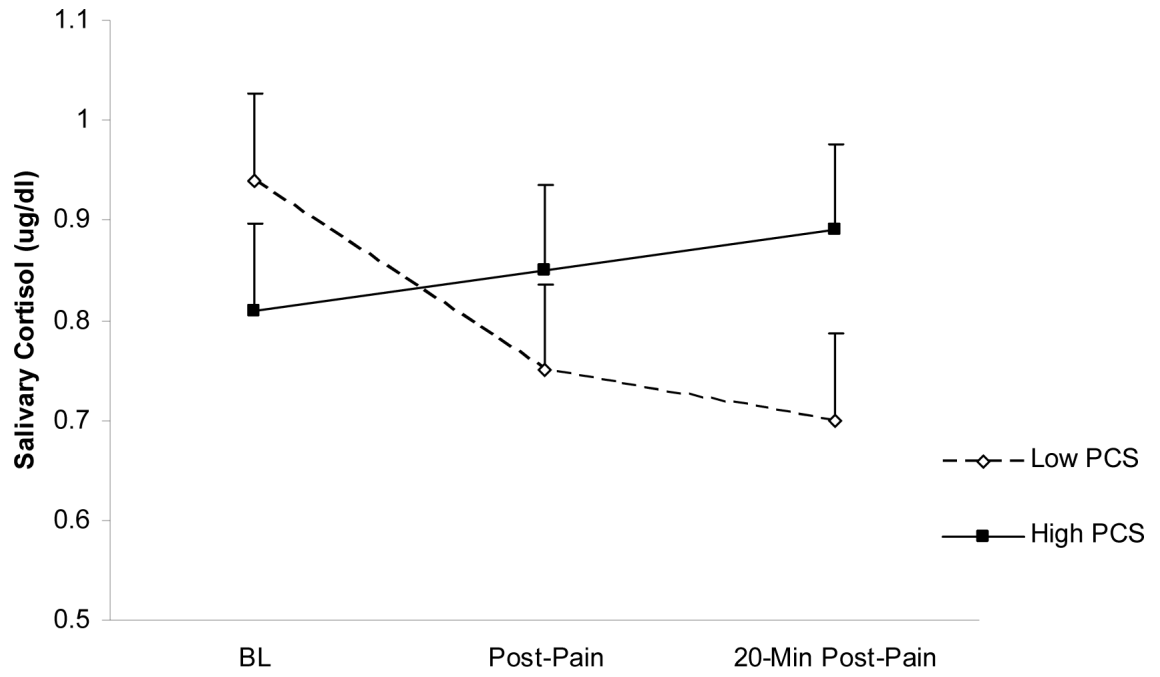
Figure 1.
Marginal means (SE) of salivary cortisol values (µg/dl) at hypothetical values of high (+1 SD) and low (−1 SD) Pain Catastrophizing Scale (PCS) scores.

Table 1

Sample characteristics.

Characteristic	TMD (n = 39)	Healthy (n = 22)
TMD Duration (in months; Mean, SD)	110.26 (103.04)	
Age (Mean, *SD*)$_a$	33.79 (12.00)	25.91 (5.76)
Sex (% Female)	82.1	95.5
Ethnicity		
Non-Hispanic White	79.5	40.9
African-American	7.7	27.3
Asian-American	7.7	22.7
Multi-Racial	5.1	4.5
Education (%)		
High School or Less	5.1	N/A
Some College	17.9	27.3
College Graduate or Greater	77	72.7
Occupational Status (% Employed)	94.9	100
Marital Status (% Married)$_a$	14	1
BMI (Mean, *SD*)	24.66 (5.08)	23.54 (4.24)
PCS (Mean, *SD*) $_a$	14.05 (8.81)	8.91 (6.77)
BSI-D (Mean, *SD*) $_a$	.33 (.34)	.08 (.17)

Note. BMI = Body Mass Index; PCS = Pain Catastrophizing Scale total scores; BSI-D = Brief Symptom Inventory – Depression subscale scores. Subscript indicates a statistically significant group difference at p < .05.

Table 2

Mean (SD) PPTh, HPTh and CPR values by pain status.

	PPTh Masseter_a	PPTh Forearm	PPTh Trapezius	HPTh	CPR (0–100)
TMD	136.70 (50.01)	247.74 (98.52)	374.25 (158.92)	43.42 (2.83)	68.41 (26.73)
Healthy	170.13 (62.62)	267.79 (92.14)	391.69 (139.47)	42.43 (3.48)	72.49 (23.68)

Note. PPTh = Pressure Pain Threshold; HPTh = Heat Pain Threshold. CPR = Cold Pressor Pain Ratings. Subscript indicates a statistically significant group difference at $p < .05$.