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Pain catastrophizing and neural responses to pain among persons with fibromyalgia

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Summary

Pain catastrophizing, or characterizations of pain as awful, horrible and unbearable, is increasingly being recognized as an important factor in the experience of pain. The purpose of this investigation was to examine the association between catastrophizing, as measured by the Coping Strategies Questionnaire Catastrophizing Subscale, and brain responses to blunt pressure assessed by functional MRI among 29 subjects with fibromyalgia. Since catastrophizing has been suggested to augment pain perception through enhanced attention to painful stimuli, and heightened emotional responses to pain, we hypothesized that catastrophizing would be positively associated with activation in structures believed to be involved in these aspects of pain processing. As catastrophizing is also strongly associated with depression, the influence of depressive symptomatology was statistically removed. Residual scores of catastrophizing controlling for depressive symptomatology were significantly associated with increased activity in the ipsilateral claustrum ($r = 0.51$, $P < 0.05$), cerebellum ($r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.47$, $P < 0.05$), and parietal cortex ($r = 0.41$, $P < 0.05$), and in the contralateral dorsal anterior cingulate gyrus (ACC; $r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.41$, $P < 0.05$), medial frontal cortex ($r = 0.40$, $P < 0.05$) and lentiform nuclei ($r = 0.40$, $P < 0.05$). Analysis of subjects classified as high or low catastrophizers, based on a median split of residual catastrophizing scores, showed that both groups displayed significant increases in ipsilateral secondary somatosensory cortex (SII), although the magnitude of activation was twice as large among high catastrophizers. Both groups also had significant activations in contralateral insula, SII, primary somatosensory cortex (SI), inferior parietal lobule and thalamus. High catastrophizers displayed unique activation in the contralateral anterior ACC, and the contralateral and ipsilateral lentiform. Both groups also displayed significant ipsilateral activation in SI, anterior and posterior cerebellum, posterior cingulate gyrus, and superior and inferior frontal gyrus. These findings suggest that pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control. These results support the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Activation associated with catastrophizing in motor areas of the brain may reflect expressive responses to pain that are associated with greater pain catastrophizing.

Keywords: catastrophizing; functional neuroimaging; fibromyalgia; pain modulation

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; fMRI = funtional MRI; IPL = inferior parietal lobule; MPQ = McGill Pain Questionnaire; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; VAS = visual analogue scale

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Introduction

The experience of pain is a multidimensional phenomenon that is influenced by multiple factors, such as affect, previous experience and cultural beliefs, in addition to sensory input (Melzack and Wall, 1982). Among persons with chronic pain, psychosocial factors may play a significant role in the development and maintenance of the disorder (Bigos *et al*., 1992; Burton *et al*., 1995; Gatchel *et al*., 1995). Psychosocial factors that probably influence the experience of pain include cognitions (i.e. thoughts, beliefs and appraisals), coping responses and social environmental variables (Jensen *et al*., 2002).

Pain catastrophizing, or responses to pain that characterize it as being awful, horrible and unbearable, is increasingly recognized as an extremely important contributor to the experience of pain. Early studies on catastrophizing suggested that these maladaptive responses to pain mirrored responses typically observed in persons with depression and proposed that catastrophizing was merely a symptom of depression rather than a separate entity (Rosenstiel and Keefe, 1983; Sullivan and D'Eon, 1990). Later studies, however, have found catastrophizing to be significantly associated with pain and pain-related disability independent of the influence of depression and negative affect (Keefe *et al*., 1989, 1990; Geisser *et al*., 1994, 2003; Geisser and Roth, 1998; Sullivan *et al*., 1998). These studies provide strong support for the notion that catastrophizing plays an important role in the experience of chronic pain independent of its observed relationship to depression. The influence of catastrophizing on pain can be substantial. Burton *et al*. (1995) observed that catastrophizing alone accounted for 47% of the variance in predicting the development of chronic pain from an episode of acute pain.

Although the mechanisms by which catastrophizing influences the experience of pain are not known (Sullivan *et al*., 2001), one hypothesis is that pain catastrophizing influences the attentional focus on painful or potentially painful events. Persons who catastrophize have difficulty shifting their focus of attention away from painful or threatening stimuli, and attach more threat or harm to non-painful stimuli (Crombez *et al*., 1998, 2002; Peters *et al*., 2000). These studies suggest that catastrophizing increases pain-related fear, which in turn increases attention to the stimulus. Thus, in addition to intensity, the threat value of the stimulus may be an important mediator of altered pain perception. There is also evidence that catastrophizing is positively associated with affective pain ratings, which in turn may lead to higher overall evaluations of the experience of pain (Geisser *et al*., 1994).

Despite the proposed importance of cognitive and emotional factors in the experience of pain, few studies have assessed the association between these factors and the neurophysiolgical mechanisms involved in pain processing. Cognitive factors associated with pain, such as catastrophizing, should be observable through methods such as functional brain imaging. Attention biases towards painful stimuli have been shown to produce unique brain activation independent of painful stimulation. For example, Brooks *et al*. (2002) found a unique pattern of insula activation when subjects shifted their attention away from the stimulated hand. Similarly, Ploghaus *et al*. (1999) found a distinct pattern of activation in the insular cortex, medial frontal cortex and cerebellum that was unique to the fear or anticipation of painful stimuli. Since previous studies have suggested that catastrophizing influences pain perception through increased attention to painful stimuli and enhanced affective and evaluative responses to pain, catastrophizing may be associated with heightened or unique activation in brain regions that modulate attention and emotional reactions to painful stimulation.

Functional imaging techniques have identified a number of brain regions that are activated with painful stimulation (Casey *et al*., 1996, 2001; Peyron *et al*., 2000). Pain stimulation is typically associated with activation in the secondary somatosensory cortex (SII), insular regions and the anterior cingulate cortex (ACC). Activation in the contralateral thalamus and primary somatosensory cortex (SI) is also observed, but less consistently. Activation of the lateral thalamus, SI, SII and insula appears to be related to the sensory discriminative aspects of pain, while the ACC may be related to the affective and attentional components of pain.

In the present study, we hypothesized that pain catastrophizing would be associated with greater activation in areas associated with the attentional and affective aspects of pain among chronic pain patients undergoing painful stimulation. We hypothesized that catastrophizing would be associated with activation in the ACC, insula, medial frontal cortex and cerebellum. As catastrophizing is often highly related to depression, and there is debate as to whether catastrophizing is a symptom of depression or a separate construct, associations between catastrophizing and brain activity were examined while statistically controlling for the influence of self-report of depressive symptoms.

Methods

Subjects

Twenty-nine patients, 19 female and 10 male, aged 18–60 years, who met the 1990 American College of Rheumatology criteria for fibromyalgia (Wolfe *et al*., 1990), were included. The study was approved by the Georgetown University Medical Center's institutional review board, and informed consent was obtained from all participants for study on the General Clinical Research Center. All patients underwent a comprehensive screening during which the diagnosis was confirmed and co-morbidities were evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g. morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e. hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g. schizophrenia, substance abuse), factors known to affect the hypothalamic–pituitary axis or autonomic function (e.g. cigarette smoking, daily intake of caffeine

exceeding the equivalent of two cups of coffee) or medication usage other than as-needed analgesics (excluding long-term narcotics).

Subjects who qualified for inclusion in the study were scheduled for a 2-day study protocol. They were asked to discontinue intake of antidepressants up to 4 weeks ahead of the appointment (depending on the drug), but were allowed to use non-steriodal anti-inflammatory drugs until 3 days before the appointment. On the first day of the study, patients completed the self-report questionnaires and were familiarized with the pain testing paradigm. On the following day, they participated in a pain psychophysical session and the functional MRI (fMRI) procedure.

Measures

Depression

The Center for Epidemiological Studies Depression Scale (Radloff, 1977) is a 20-item self-report questionnaire that assesses symptoms of depression in non-psychiatric adults. This instrument possesses strong psychometric properties and has demonstrated strong associations with other measures of depressive symptoms (Hertzog *et al*., 1990). The scale has acceptable validity among persons with physical disabilities (Berkman *et al*., 1986), and studies indicate that the measure has good predictive validity for identifying depression among persons with chronic pain (Turk *et al*., 1994; Geisser *et al*., 1997).

Catastrophizing

Catastrophizing was assessed using the catastrophizing subscale from the Coping Strategies Questionnaire (Rosenstiel and Keefe, 1983). The Coping Strategies Questionnaire assesses the frequency of patients' use of pain coping strategies. There are seven subscales consisting of six cognitive strategies (diverting attention, reinterpreting pain sensations, ignoring pain sensations, coping self-statements, praying or hoping, and catastrophizing) and one behavioural strategy (increasing activity level). Subjects use a 7-point scale to rate how often they use each strategy to cope with pain. Subjects are also asked to make two ratings of their appraisal of the overall effectiveness of coping strategies (how much control they have over pain and how much they are able to decrease pain). Reliability coefficients for each of the subscales range from 0.71 to 0.85 (Rosenstiel and Keefe, 1983).

Clinical pain

Clinical pain experience of subjects was assessed using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987). This questionnaire contains 15 pain adjectives. The author reports that the scale is sensitive to change produced by various pain interventions, and is highly correlated with the parent scale (Melzack, 1987).

Self-report of clinical pain intensity was also obtained by asking subjects to rate their pain during the past week on a visual analogue scale (VAS). The scale was 100 mm long and anchored by the statements 'no pain' on the left and 'the most intense pain imaginable' on the right. Separate VAS scales were used to measure subjects' level of pain on the day of testing, pain in the past month, pain intensity on bad days and pain intensity on good days. VAS ratings have demonstrated good reliability (Revill *et al*., 1976; Boeckstyns and Backer, 1989) and concurrent validity when compared with other methods of pain measurement (Downie *et al*., 1978; Jensen *et al*., 1989).

Experimental pain assessment

During the pain testing session, pressure pain sensitivity was evaluated by subjective scaling of multiple pressure pain sensations of suprathreshold intensities. Discrete 5 s pressure stimuli were applied to the fixated left thumbnail with a 1 cm^2 hard rubber probe. Previous studies have shown that 'neutral' regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity (Petzke *et al*., 2003). The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform. Subjects rated the intensity of pressure pain sensations using a combined numerical analogue descriptor scale, developed from previously quantified verbal descriptors (Gracely *et al*., 1979). The session began with a series of stimuli presented in a predictable, 'ascending' fashion, beginning at 0.5 kg/cm^2 and increasing in 0.5 kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2. Following the ascending series, 36 stimuli were delivered at 20 s intervals in random order, using the multiple random staircase method (Gracely *et al*., 1988). The multiple random staricase method is response-dependent, i.e. it determines the stimulus intensity needed to elicit a specified response. In this study, we determined the stimulus intensities sufficient to elicit pain threshold, mild pain (7.5 out of 21 scale units) and slightly intense pain (13.5 out of 21 scale units).

Functional imaging

MRI and fMRI scans were performed on a 1.5 T vision system (Siemens, Munich, Germany). A T1-weighted MRI anatomical scan session [echo time (TE) 4 ms; recovery time (TR) 9.7 ms; flip angle 12°; 256 × 256 pixel matrix; field of vision (FOV) 256 mm; 1 mm^3 voxels, acquired non-interleaved in the sagittal direction] was followed by two functional scan sessions using multi-slice, echo-planar imaging fMRI acquisition (TE 40 ms; TR 5 s; repetition time 5 s; flip angle 90°; 64 × 64 pixel matrix; FOV 192 mm; 50 horizontal 3 mm slices). These parameters allowed coverage of the entire brain with 3 mm^3 voxels within 5 s.

During each fMRI session, the first three scans were discarded to allow for saturation of the tissue. Starting on the fourth scan, pressure stimuli of 25 s duration ('on' condition) were alternated with 25 s resting periods ('off' condition). Onset and offset of a stimulus was coincident with the beginning of a scan, allowing the acquisition of five scans during each of 12 'on' and 12 'off' conditions.

During the 'on' condition, different stimulus intensities were presented in random sequence. These stimulus intensities included three stimuli chosen on the basis of the baseline pain testing, sufficient to elicit a rating of 13.5 out of 20 (slightly intense pain). The analysis was performed on the scans acquired during the slightly intense pain conditions and the 'off' conditions.

Imaging analysis

Imaging data were analysed with MEDx (Sensor Systems, Sterling, VA). The functional images were corrected for head motion and intensity differences. Head motion was determined by motion detection software and visual inspection of raw and processed images. Head motion greater than a half a voxel was deemed *a priori* to be unacceptable, and images meeting this criterion were to be excluded. None of the scans had head motion exceeding this

criterion, so all images were included in the analyses. Acceptable motion-corrected images were spatially smoothed at 6 mm full width at half maximum.

The brain volumes collected during 'on' conditions were compared with the brain volumes collected during 'off' conditions by *t* test. Resultant *Z* statistical volumes and mean differences volumes were registered into standardized space using the statistical parametric mapping (SPM96) echo-planar imaging template and re-sliced to 2 mm^3 voxels.

Anatomic regions were identified (i) by inspection of individual functional images superimposed on an individual structural image; and (ii) by conversion of the coordinates to the coordinate system of the Talairach–Tournoux atlas and localization using this atlas (Talairach and Tournoux, 1988) and automated software (Lancaster *et al*., 2000).

Results

The first step in the data analyses involved examining the relationship between Coping Strategies Questionnaire catastrophizing scores and scores on the Center for Epidemiological Studies Depression Scale. The correlation was marginally significant ($r = 0.36$, $P = 0.06$). To statistically control for self-reported depression in catastrophizing scores, standardized residuals were calculated by regressing Center for Epidemiological Studies Depression Scale scores on the catastrophizing scores of the Coping Strategies Questionnaire. The remaining analyses examining the relationship between catastrophizing and brain activity used these standardized residuals.

The relationship between pain catastrophizing and brain activity was examined in two ways. First, correlation coefficients were computed between the standardized residual catastrophizing scores, demographic information, clinical and experimental pain, and brain activity. Pearson correlations were examined between continuous data elements, while a Spearman ρ correlation was computed to examine the relationship between residual catastrophizing scores and gender.

To determine if the findings of the correlational analysis could be replicated utilizing a different methodological approach, a second analysis was performed classifying subjects as high and low catastrophizers based on a median split of the residual catastrophizing scores. The median residual catastrophizing score in the sample was –0.15 (range –2.41 to 4.6). Fifteen subjects who had a residual score of –0.15 or less were classified as low catastrophizers, while 14 subjects with a higher score were designated as high catastrophizers. Group differences were examined using *t* tests for continuous dependent variables, and a χ^2 analysis was performed to examine group differences in terms of gender.

Correlational analyses

The associations between catastrophizing and pain and demographic variables are presented in Table 1. Catastrophizing was not significantly associated with age and gender nor with experimental forms of pressure pain (i.e. pain threshold, mild or slightly intense). Residual catastrophizing scores were significantly related to clinical pain, as higher scores were significantly associated with higher affective and total pain ratings on the MPQ short form ($r = 0.63$, $P < 0.001$ and $r = 0.41$, $P = 0.03$, respectively), but were not significantly associated with sensory ratings. Residual catastrophizing scores were significantly associated with VAS ratings of pain during the past month ($r = 0.37$, $P = 0.05$), and on bad days ($r = 0.50$, $P < 0.01$). No significant associations were observed between catastrophizing and either ratings of pain on the day of testing or level of pain on good days.

Table 1 *Correlations between catastrophizing and demographic and pain variables*

Variable	Pearson correlation coefficient
Age	–0.34
Sex	0.03
MPQ sensory	0.30
MPQ affective	0.63***
MPQ total	0.41*
VAS today	0.28
VAS past month	0.37*
VAS pain on bad days	0.50**
VAS pain on good days	0.16
Pressure pain threshold (low; kg/cm^2)	–0.03
Pressure pain moderate (medium; kg/cm^2)	–0.23
Pressure pain slightly intense (high; kg/cm^2)	–0.01

***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

Despite catastrophizing being unrelated to reports of evoked pain, it was associated with brain activity during slightly intense pain stimulation (Table 2). Activation is expressed as the *Z* change score comparing activity during slightly intense pain stimulation with the baseline condition. Higher catastrophizing scores were significantly associated with greater activation in the ipsilateral claustrum ($r = 0.51$, $P < 0.01$), ipsilateral medial frontal gyrus ($r = 0.47$, $P < 0.01$), ipsilateral cerebellum ($r = 0.43$, $P < 0.01$), ipsilateral postcentral gyrus (SII; $r = 0.41$, $P < 0.01$) and the ipsilateral middle frontal gyrus ($r = 0.41$, $P < 0.01$). Catastrophizing was both significantly and positively associated with activation in the contralateral hemisphere in the anterior ACC ($r = 0.43$, $P < 0.01$), medial/posterior ACC ($r = 0.41$, $P < 0.01$), medial frontal gyrus ($r = 0.40$, $P < 0.01$) and lentiform ($r = 0.40$, $P < 0.01$).

Group analyses

Examining the demographic and pain variables, the groups of high and low catastrophizers did not differ significantly in terms of age or gender, nor did they differ significantly in their perception of experimental pressure pain. The groups did differ significantly on the measures of clinical pain, as

Table 2 *Significant correlations between catastrophizing and brain activation during painful stimulation controlled for depression*

Brain region	Coordinates			Pearson *r*
	x	*y*	*z*	
Ipsilateral claustrum	–30	6	5	0.51*
Ipsilateral middle frontal gyrus (BA 6)	–46	3	51	0.47*
Ipsilateral cerebellum	–30	–68	–37	0.43*
Contralateral ACC (BA 32)	8	15	36	0.43*
Ipsilateral postcentral gyrus (SII)	–63	–21	14	0.41*
Ipsilateral middle frontal gyrus (BA 11)	–30	44	–12	0.41*
Contralateral ACC (BA 24)	2	11	27	0.41*
Contralateral medial frontal gyrus (BA 6)	2	–17	56	0.40*
Contralateral lentiform	14	6	3	0.40*

*$P < 0.01$.

Table 3 *Mean (SD) of high and low catastrophizing groups on age and pain measures*

Variable	Group		*t* value
	Low	High	
Age (years)	44.6 (8.8)	38.9 (10.6)	1.57
MPQ sensory	6.5 (5.0)	12.8 (6.3)	3.0*
MPQ affective	1.8 (1.6)	3.9 (2.0)	3.1*
MPQ total	8.1 (6.2)	16.7 (7.5)	3.4*
VAS today (mm)	39.3 (29.3)	65.0 (14.9)	2.9*
VAS past month (mm)	45.3 (20.8)	67.9 (7.5)	3.8*
VAS pain on bad days (mm)	69.0 (17.9)	87.5 (8.9)	3.5*
VAS pain on good days (mm)	18.3 (14.4)	37.5 (15.9)	3.4*
Pressure pain threshold (kg/cm^2)	1.0 (0.7)	0.9 (0.6)	0.6
Pressure pain moderate (kg/cm^2)	3.0 (1.4)	2.0 (1.0)	2.0
Pressure pain slightly intense (kg/cm^2)	4.6 (1.7)	4.2 (2.2)	0.6

*$P < 0.01$.

high catastrophizers had significantly higher scores on the sensory ($t = 3.0$, $P < 0.01$), affective ($t = 3.1$, $P < 0.01$) and total ($t = 3.4$, $P < 0.01$) pain rating indexes of the MPQ short form. High catastrophizers also rated their clinical pain higher on the day of testing ($t = 2.9$, $P < 0.01$), during the past month ($t = 3.8$, $P < 0.01$), on bad days ($t = 3.5$, $P < 0.01$) and on good days ($t = 3.4$, $P < 0.01$).

Regions with increased fMRI signal in response to slightly intense painful pressure are presented in Table 4 for high and low catastrophizers. Corrected for multiple comparisons, a *Z* score of 3.5 corresponded to a *P* value of 0.05. *Z* scores of $\geqslant 3.5$ were determined as significant activation in a region. Both groups displayed significant increases in fMRI signal in contralateral insula, SI, SII, inferior parietal lobule (IPL) and thalamus, and in ipsilateral SI, SII anterior cerebellum, posterior cerebellum, posterior cingulate gyrus, superior frontal gyrus and inferior frontal gyrus. Note that the activation in ipsilateral SII was twice as large among high catastrophizers.

In addition to activations common to both groups, activations in several regions were observed only in the high catastrophizing group. These data are presented in Table 5. High catastrophizers displayed activation in the contralateral anterior ACC, and in both the contralateral and ipsilateral lentiform. There were no such unique activations in the low catastrophizing group.

Table 6 shows the results of a *t* test of the mean differences in fMRI signal in response to slightly intense painful pressure between both groups. Patients scoring high in catastrophizing displayed six regions with a significantly higher increase in fMRI signal: ipsilateral SII, ACC, superior frontal gyrus, medial frontal gyrus, premotor cortex and contralateral IPL. Three of these areas (ipsilateral SII, middle and medial frontal gyrus) corresponded to areas associated with the level of catastrophizing. Two of these areas (ipsilateral SII and contralateral IPL) corresponded to areas that showed significantly increased fMRI signal in response to slightly intense pain in both groups (Table 4). On the other hand, patients scoring low in catastrophizing displayed a significantly higher increase in fMRI signal only in ipsilateral IPL.

Discussion

The results support our hypothesis that pain catastrophizing, independent of self-report of depressive symptoms, is associated with the magnitude of neural activation evoked by

Table 4 *Brain areas commonly activated in high and low catastrophizing groups*

Brain region	Coordinates			*Z* score
	x	*y*	*z*	
Ipsilateral SII (BA 40)				
High	–69	–20	18	7.31
Low	–61	–20	21	3.58
Ipsilateral SI (BA 2)				
High	–63	–25	36	4.99
Low	–69	–24	34	5.82
Ipsilateral cerebellum anterior lobe				
High	–36	–54	–26	5.96
Low	–32	–54	–26	5.14
Ipsilateral cerebellum posterior lobe				
High	–36	–69	–23	5.25
Low	–30	–65	–20	5.31
Ipsilateral posterior cingulate gyrus				
High	–4	–22	27	4.04
Low	–4	–20	34	3.61
Ipsilateral superior frontal gyrus (BA 6)				
High	–6	24	58	4.25
Low	–16	12	51	3.22
Ipsilateral inferior frontal gyrus				
High	–53	8	14	4.63
Low	–63	13	23	3.94
Contralateral insula (BA 13)				
High	46	2	5	5.24
Low	38	4	9	5.24
Contralateral SII (BA 40)				
High	61	–20	19	6.16
Low	65	–24	21	4.80
Contralateral inferior parietal lobule (BA 40)				
High	51	–32	55	4.00
Low	53	–40	52	3.51
Contralateral SI (BA 2)				
High	61	–17	43	5.02
Low	55	–16	38	4.97
Contralateral thalamus				
High	8	–11	4	3.36
Low	4	–11	8	4.48

painful stimulation. Correlational analyses showed an association between catastrophizing and pain-evoked activation in the bilateral dorsolateral prefrontal cortex, ipsilateral claustrum, cerebellum and parietal cortex, and contralateral rostral anterior cingulate gyrus, medial frontal cortex and lentiform. Group analyses based on a median split of residual pain catastrophizing scores indicated that persons both high and low on catastrophizing displayed a similar pattern of activations in the contralateral SI, SII, insula, thalamus and IPL, and the ipsilateral SI, SII, cerebellum, rostral ACC and dorsolateral prefrontal cortex. This pattern is consistent with the cerebral response to pressure pain reported recently using similar stimulus parameters (Gracely *et al*., 2002). Neuronal activation in ipsilateral SII, however, was more than twice as large in subjects high on catastrophizing compared with subjects low in catastrophizing. In addition, high catastrophizers displayed unique activation in the contralateral rostral ACC, and ipsilateral and contralateral lentiform. Figure 1 shows that the location of the unique activation of the contralateral ACC in the group analysis was very close to the region that was associated with catastrophizing in the correlational analysis.

As hypothesized, catastrophizing demonstrated significant relationships with activation in brain structures that have been found to be associated not only with pain processing, but also with the attentional and emotional aspects of pain. In addition, catastrophizing was associated with activation in the premotor cortex and in the lentiform nuclei. This latter activation is consistent with previous research suggesting that catastrophizing is associated with greater pain behaviour and increased emotional expression in response to pain (Sullivan *et al*., 2001). Consistent with the studies mentioned earlier, catastrophizing was associated with greater activation in the cerebellum and medial frontal gyrus. These regions were among those identified as uniquely activated during anticipation of pain (Ploghaus, 1999), although, in the present study, activity in the insula was not uniquely associated with catastrophizing. In addition, activation was observed in areas

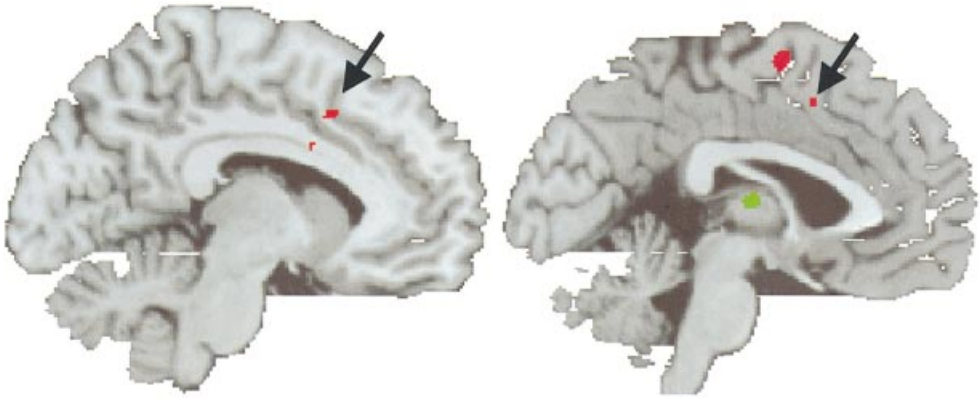

Fig. 1 Examples from association and group analyses. Significant influence of catastrophizing on activity in the contralateral rostral ACC (BA 32) is shown in red for the association analysis (left, Table 2) and for the group scoring high in catastrophizing (right, Table 5). The green region in the right figure shows common activation in the thalamus in both high and low catastrophizing groups (Table 4).

Table 5 *Brain areas uniquely activated in the high catastrophizing group*

Brain region	Coordinates			*Z* score
	x	*y*	*z*	
Contralateral ACC (BA 32)	4	12	40	4.02
Ipsilateral lentiform	–14	4	5	4.36
ContralateraI lentiform	22	6	3	3.76

uniquely associated with catastrophizing in the SII and the rostral ACC. The dorsal, rostral ACC may be preferentially involved in cognition functions (e.g. selective attention), while the ventral, perigenual portion may be more involved in emotional processing (Davidson *et al*., 2002). Expectation of pain has been associated with increased activity in SII (Sawamoto *et al*., 2000), and the anterior ACC is activated during attention-demanding tasks (Davis *et al*., 2000). Activation of these stuctures further suggests that catastrophizing may influence pain perception through its influence on attention.

Although catastrophizing was significantly associated with clinical pain, it was not associated with differences in experimental pain perception. This suggests that the fMRI findings are not due to differences in the intensity of the simulation used during scanning. While one might predict that catastrophizing might be associated with heightened perception of experimental pain, as shown in previous studies in normals and clinical populations (Geisser *et al*., 1992, 2003), we believe that the lack of a relationship between catastrophizing and experimental pain is due to the experimental pain methods used to determine the stimulus intensities. Petzke *et al*. (2003) propose that experimental methods that employ gradually ascending methods of stimulation are more likely to be subject to biases produced by psychological factors. The authors compared four different methods of experimental pain stimulation methods, and contrasted gradually ascending methods with those employing the random staircase method utilized in the present study. The authors found that experimental pain measures that employed gradually ascending methods of stimulation were significantly correlated with measures of psychological distress, while assessment of experimental pain utilizing the random staircase method was not. However, all the measures were significantly associated with clinical pain. These findings suggest that perceived pain intensity as determined by the random staircase method is less likely to be influenced by psychological factors such as catastrophizing, and suggest that this measure is more reflective of the sensory aspect of pain and less susceptible to the influence of factors reflecting the affective and evaluative components of pain. This is consistent with the finding that catastrophizing in the present study was associated primarily with structures involved in the affective and evaluative aspects of pain processing, as discussed further below. While unique patterns of activation associated with catastrophizing are evident during stimulation, the methodology used to determine pain ratings in the present study minimized the influence of the catastrophizing on the determination of these values.

In addition, the influence of catastrophizing on pain perception may be modulated by the perceived threat value of the stimulus. For example, studies examining perceptual differences among patient groups that use paradigms that do not involve the administration of noxious stimuli (e.g. Peters *et al*., 2000) have not observed a relationship between catastrophizing and perception. Thus, it is also possible that the threat value of the stimuli utilized in the present study was low, attenuating a relationship between catastrophizing and the perception of experimental pain.

The regions found to be associated with catastrophizing in this study include not only structures involved in emotional or attentional processing of painful stimuli, but also sensory structures that are likely to be involved in encoding the magnitude of evoked pain sensations. Activity in SI and SII has been shown to be associated with the magnitude of pain evoked by contact heat (Coghill *et al*., 1999) and, in our own laboratory, we have found that the magnitude of painful

Table 6 *Brain regions showing significantly higher activations in one of the groups*

Group	Brain region	Coordinates			*Z* score
		x	*y*	z	
High	Ipsilateral SII	–69	–22	18	3.45*,+
	Ipsilateral ACC (BA 32)	–14	15	36	3.33
	Ipsilateral superior frontal gyrus (BA 11)	–20	59	–21	3.24
	Ipsilateral medial frontal gyrus (BA 6)	–48	–1	52	3.52*
	Contralateral medial frontal gyrus (BA 6)	2	–13	52	4.00*
	Contralateral IPL (BA 40)	53	–26	31	3.58+
Low	Ipsilateral IPL (BA 40)	–48	–46	58	3.79

*Corresponds to Table 2; +corresponds to Table 4.

pressure is associated with activity in SI and SII (Grant *et al*., 2001). The association found between brain activity and catastrophizing, however, was not limited to somatosensory regions but also included the ACC. Both the ACC and SII may be involved in evaluative or affective processing, suggesting that catastrophizing is associated with the affective and evaluative aspects of pain. Thus, activation in SII associated with catastrophizing in the present study probably reflects an assocation between catastrophizing and affective and evaluative pain processing, as catastrophizing was not related to activation in SI. This is supported in the present study through the unique patterns of activation observed and by the fact that catastrophizing was more highly associated with the affective and total subscales of the MPQ short form, replicating findings from a previous study (Geisser *et al*., 1994).

It should be noted that the study design was cross-sectional, and therefore no conclusions can be made regarding cause–effect relationships. Although it is possible that pain catastrophizing may occur in response to pain, in the present study, catastrophizing was assessed prior to fMRI evaluation, suggesting that catastrophizing was not a reaction to experimental pain stimulation. In addition, it is possible that findings may be related to the influence of other variables associated with catastrophizing, such as clinical pain. In the group analyses, the high and low catastrophizing groups differed significantly on ratings of clinical pain on the day of testing. However, these differences in clinical pain ratings may be due to the influence of catastrophizing, as many clinical pain measures are impacted by affective and evaluative responses to pain. For example, Clark *et al*. (2002) found that a unidimensional pain rating scale, similar to the one used in the present study, was significantly associated with categories of affective pain desciptors, but not significantly associated with sensory pain descriptors.

While we observed group differences in clinical pain on the day of testing, catastrophizing was not significantly correlated with this variable. This suggests that it is unlikely that the findings of the correlational analyses are spuriously due to the influence of clinical pain. In addition, while catastrophizing was associated with activation in some structures that are uniquely associated with clinical pain states, no relationship was observed between catastrophizing and other structures known be differentially activated in clinical pain populations, such as SI. For example, Flor *et al*. (1995), found that activation in primary somatosensory cortex correlated very highly (r = 0.93) with clinical pain among persons with phantom limb pain. Thus, we believe the pattern of findings observed in the group analysis are probably not due to differences in clinical pain intensity.

Given that catastrophizing and clinical pain tend to covary, it would be beneficial for future studies to examine whether interventions that selectively influence catastrophizing or clinical pain uniquely alter cerebral patterns of pain activation. However, since these variables may be intrinsically linked, it may be difficult to find interventions that selectively influence clinical pain without altering catastrophizing, or vice versa. Alternatively, it might be beneficial to study the relationship between catastrophizing and pain activation in normal, healthy populations, as catastrophizing has also been found to influence pain perception in these populations (Geisser *et al*., 1992).

In summary, catastrophizing appears to be uniquely associated with activation in brain areas involved in attention to pain, emotion and motor activity. The findings support the hypothesis that catastrophizing influences pain perception through its influence on affective and attentional responses to pain. It would be beneficial to examine whether brain responses to pain among persons who are high in catastrophizing can be altered through manipulations designed to change the threat value of the stimulus, or attention to the stimulus. The findings also suggest that interventions designed to alter attention to or the perceived threat of clinical pain may be beneficial among persons with pain who catastrophize about their condition.

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