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Cortical responses to pain in healthy individuals depends on pain catastrophizing

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Abstract

The personal experience of pain is complex and depends on physiological and psychological factors. From this latter category, pain catastrophizing plays an important role in pain behavior and response. We aimed to determine the effect of pain catastrophizing on central nociceptive processing in healthy individuals. Functional MRI was performed during two pain intensity levels evoked by electrical median nerve stimulation in 22 healthy individuals. Pain catastrophizing scores were determined for all subjects. Pain catastrophizing was not related to activity in regions associated with sensory-discriminative aspects of pain, such as the primary or secondary somatosensory cortex. Instead, during mild pain, there was a relationship between catastrophizing and activity in cortical regions associated with affective, attention, and motor aspects of pain, including dorsolateral prefrontal, insula, rostral anterior cingulate, premotor, and parietal cortices. During more intense pain, prefrontal cortical regions implicated in the top-down modulation of pain were negatively correlated with catastrophizing. These findings can be viewed from the framework of an attention model of pain catastrophizing, whereby a cortical vigilance network is engaged during mild pain, but diminished prefrontal cortical modulation impedes disengaging from and suppressing pain during more intense pain. These findings may also implicate catastrophizing in the progression to or persistence of chronic pain.

Keywords: Coping; fMRI; Neuroimaging; Modulation; Vigilance

1. Introduction

Psychological variables can shape the subjective experience of pain. However, it is unclear how such factors relate to central neural processing of nociceptive stimuli in healthy individuals. Pain catastrophizing, a maladaptive response to pain characterized by an experience of heightened pain intensity (Sullivan et al., 2001), increased disability (Sullivan et al., 2005), and difficulty disengaging from pain (Van Damme et al., 2004), is an example of a psychological measure that can affect the pain experience. Although it does show a relationship to pain affect and the personality trait neuroticism, pain catastrophizing contributes uniquely to the pain experience in healthy individuals (Sullivan et al., 1995) as well as in people with chronic pain (Goubert et al., 2004). Pain catastrophizing scores can predict individuals' pain sensitivity, how they cope with pain in terms of mental and physical disability, and their quality of life (Martin et al., 1996; Petrak et al., 2003; Severeijns et al., 2001, 2002; Turner et al., 2002; Woby et al., 2004). Furthermore, pre-surgery pain catastrophizing scores can predict post-surgical pain (Edwards et al., 2004; Pavlin et al., 2005), suggesting that some individuals may be predisposed to developing and/or maintaining chronic pain. Finally, there is evidence that catastrophizing is

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related to pain vigilance in people with chronic pain (Goubert et al., 2004; Roelofs et al., 2003). In fact, in patients with heightened vigilance to pain, this vigilance is in part mediated by catastrophic thinking about pain (Crombez et al., 2004).

Several models provide a framework for pain catastrophizing (see Sullivan et al., 2001). The finding that persons with high catastrophizing scores have difficulty suppressing pain-related thoughts and behaviors (e.g., Crombez et al., 1998; Van Damme et al., 2004) led to the formation of the "attention model". This model proposes that attention to pain underlies pain catastrophizing. The attention model of pain catastrophizing is also supported by neuroimaging data in subjects with chronic pain (fibromyalgia), showing a correlation between catastrophizing scores and activity in the dorsolateral prefrontal cortex (DLPF), rostral anterior cingulate cortex (ACC), and medial prefrontal cortex (MFC) (Gracely et al., 2004), cortical regions implicated in pain vigilance, attention, and awareness (Bornhovd et al., 2002; Buchel et al., 2002; Derbyshire et al., 1997; Valet et al., 2004).

In the current study, we tested the hypothesis that in normal healthy people, pain catastrophizing is related to activity in: (1) brain regions activated by pain and (2) brain regions related to vigilance. To test these hypotheses, we determined in healthy subjects the relationship between individual pain catastrophizing scores and pain-evoked cortical responses using functional MRI (fMRI).

2. Methods

2.1. Subjects

Twenty-two healthy subjects (10 male, 12 female), 25 ± 4 years old (mean $\pm$ SD), were recruited for the study and consented to procedures approved by the University Health Network Research Ethics Board. All subjects were medication free at the time of scanning and reported no prolonged pain, neurological or psychiatric history.

2.2. Measures

The study consisted of two sessions on separate days. The first session included fMRI. In the second session, the fMRI session protocol was replicated outside of the scanner, and subjects completed the McGill pain questionnaire short form (MPQ-SF; Melzack, 1987), the NEO-AC five-factor personality index (Costa and McCrae, 1992), of which neuroticism is one sub-scale, and the pain catastrophizing scale (PCS; Sullivan et al., 1995). The MPQ-SF was completed while moderate pain (see below) was being invoked, and included both sensory words (e.g., "shooting", "sharp", and "cramping") and affective words (e.g., "sickening", "fearful", and "punishing-cruel"). In completing the PCS, subjects were instructed to consider their reactions to pain experiences in general, and not focus on one specific event. A total PCS score was calculated from the summed response to all questions. Relationships between MPQ-SF affective and sensory, transcutaneous electrical nerve stimulation (TENS) current (see below), neuroticism, and PCS scores were determined by statistical correlation.

2.3. Experimental pain

Pain was evoked via transcutaneous electrical nerve stimulation (TENS; EMPI 300PV) of the left median nerve (Seminowicz et al., 2004) using a square wave asymmetric pulse (200 μs) at 35 Hz. Pain intensity was rated on a verbal scale of 0 (no pain) to 100 (extremely intense pain). In each subject, two TENS current levels were determined prior to fMRI: one level that consistently evoked a pain intensity rating of ~20 and another that evoked a rating of ~60. These levels were used in the MRI session and will henceforth be referred to as "mild" and "moderate" pain. The mean mild TENS current was 18.1 ± 4.88 (SD) mA, and the mean moderate TENS current was 25.6 ± 6.93 mA.

Subjects did not rate pain during the MRI session. However, in the second experimental session, subjects rated pain intensity and unpleasantness using a verbal numerical rating scale after each block of task. Subjects were randomly asked to rate pain intensity or unpleasantness on the same scale described above or were not asked to rate anything. Subjects were instructed to concentrate on task performance during this session.

2.4. Functional imaging

Subjects underwent fMRI on a 1.5 T Echospeed MRI system (GE Medical Systems, Milwaukee, WI) fitted with a standard quadrature head coil. Three experimental runs of 9 min, 44 s were performed, with a short rest between runs. A high-resolution three-dimensional anatomic scan of the whole head (124 sagittal slices; 256×256 matrix, 24×24 cm field of view, and $1.5 \times 1.07 \times 1.07$ mm voxels) was obtained using a T1-weighted 3D spoiled gradient echo (SPGR) sequence (flip angle = 45°, echo time (TE) = 5 ms, and repetition time (TR) = 25 ms). Whole brain functional imaging used one-shot spiral gradient echo imaging of 25 axial slices ($T2^*$-weighted; flip angle = 80°, TE = 40 ms, TR = 2000 ms, 64×64 matrix, 20×20 cm FOV, and $3.125 \times 3.125 \times 4$ mm voxels). A total of 295 functional volumes were acquired for each run; the first three scans were removed to allow signal equilibration.

The fMRI experiment was a block design to examine the effects of mild and moderate pain. The protocol compared functional data acquired during a simple 12 s "OFF" (no stimulation) block to a subsequent 14 s "ON" (pain stimulation) block. Throughout both block types, subjects performed a control tapping task (see below). Therefore, during each functional run, 12 s "baseline" (tapping, no stimulation) blocks were interleaved with 14 s "pain condition" blocks. The fMRI design is shown in Fig. 1. During the pain condition blocks, mild or moderate painful stimuli were delivered while subjects performed a tapping task which served to engage all subjects in a motor control. The simple tapping task required subjects to press a button on a MR-compatible button box (Rowland Institute of Harvard, Cambridge, MA) to indicate the sequential position of an asterisk viewed on a screen through a head-coil mounted mirror. The asterisk moved from left to right on the screen and the subjects responded to the position of the

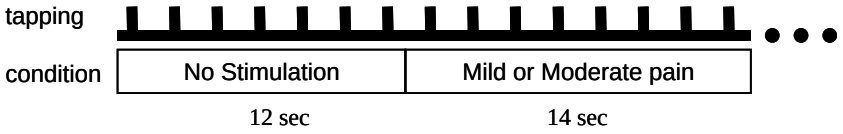

Fig. 1. fMRI paradigm. Vertical bars indicate when a stimulus appeared on the screen, to which subjects responded with an appropriate button press. Mild or moderate painful stimulation conditions followed a "baseline" period of no stimulation. Each condition was repeated a total of six times per subject. Other cognitive task conditions were also performed in this experiment, but the data are not shown here.

asterisk with the button corresponding to that position. This simple reaction time task has minimal cognitive demand and does not include cognitive conflict. Each block appeared twice per run, for a total of six times per subject.

This study was part of a larger experimental protocol to investigate pain–cognition interactions. Thus, each run also included additional block conditions not included in the present analyses. These additional blocks included the performance of a cognitive task, the multi-source interference task (MSIT; Bush et al., 2003), at three levels of difficulty, that involved delivering 1500 ms stimuli appearing every 1750 ms followed by a blank screen for 250 ms.

2.5. Analysis

Brainvoyager QX (Brain Innovation, Maastricht, The Netherlands) versions 1.1.6 and 1.2.6 were used for preprocessing and data analysis of the functional data, respectively. Preprocessing included, in the following order: motion correction, slice timing correction, linear trend removal, high pass filtering at 3 cycles per run, and smoothing to 6 mm FWHM. Datasets were interpolated to $3 \times 3 \times 3$ mm, aligned to the anatomical image, and transformed to Talairach space. Reported voxels are $1 \times 1 \times 1$ mm.

Data analysis involved two stages: (1) The first stage delineated a general map of pain-related activations from a random effects, voxel-by-voxel, general linear model (GLM) analysis with all subjects. A z-score transformation was performed across subjects so that baseline levels of signal did not affect the results. Pain-related activations were determined from the contrasts of moderate and mild pain minus no stimulation at a false discovery rate corrected threshold of $p < 0.001$, then restricting cluster size to a minimum of 150 mm^3. The peak activity of each region identified in this analysis was then tested for correlation to the PCS scores across individuals. (2) The second stage used a regression analysis approach to directly delineate a correlation map between catastrophizing and pain-evoked activity across individuals. In this step, we ran the same GLM analyses as above, but this time used a covariate of PCS scores, such that we could identify a pattern of activity related to PCS scores, within the context of pain. This analysis was performed separately for moderate pain and mild pain (each minus no stimulation). We set a threshold of $p < 0.05$ for the overall F map. Then, in order to determine the effects of catastrophizing independent of other related variables, the regions identified in these covariate analyses were submitted to a multiple regression with PCS, TENS current level, and neuroticism. This way, significant partial correlations for PCS were determined, and we could conclude that catastrophizing contributed significant, unique variance to activity in these regions.

3. Results

3.1. Pain catastrophizing scores

The pain catastrophizing scale scores ranged from 5 to 32 out of a possible range of 0–52. The mean score was 17.3 ± 7.87 (SD), with a median score of 18, similar to what has been reported in other samples of healthy individuals (Sullivan et al., 1995, 2004; Van Damme et al., 2004). PCS scores in people with chronic pain are generally slightly higher (Sullivan et al., 1998, 2005; Sullivan and Stanish, 2003), but there is a large overlap in scores between healthy individuals and those with chronic pain.

3.2. Whole group analysis

The stage 1 random effects GLM contrast of "moderate pain minus no stimulation" and "mild pain minus no stimulation" revealed activation within cortical areas typically associated with pain, including the primary and secondary somatosensory cortices (S1, S2), caudal anterior cingulate cortex (ACC), insula, and prefrontal cortex (areas 9 and 45) (Table 1). However, the activity within these regions did not correlate significantly with individual PCS scores (Table 1, right column).

3.3. Correlation analyses

PCS scores were strongly correlated to the neuroticism scores ($r = 0.72$, $p < 0.001$) and also moderately correlated with the number of affective words chosen ($r = 0.42$, $p < 0.05$), and current levels required to evoke pain ($r = -0.43$ for mild and -0.46 for moderate pain, $p < 0.05$). The relationship between MPQ and PCS scores, and TENS current levels and PCS scores is shown in Fig. 2.

Because of the well-known relationship between neuroticism, pain intensity ratings, and catastrophizing, following the stage 2 direct regression analysis of the pain activations with PCS scores, multiple regression with neuroticism, TENS current level, and PCS was performed to reveal the independent contributions of PCS to regional activity (Table 2, Fig. 3). Only regions with significant independent contributions from PCS were included in the results. Representative examples of the correlation between PCS and pain-evoked cortical activity are shown in Fig. 4.

Table 1
Pain-related activations for moderate and mild pain evoked by left median nerve stimulation, and correlations of the peak voxel BOLD response with PCS

	BA	R/L	*X*	*Y*	*Z*	Whole group *t*-value	Correlation with PCS *r*-value
Mild pain							
S1	3, 1, 2	R	34	−29	56	6.82	0.25
S2	40	R	43	−26	21	6.16	0.201
S2	40	L	−56	−15	22	5.91	0.234
Caudal ACC	24	R	9	−8	34	7.20	0.351
Mid-insula		R	37	−4	18	5.11	−0.098
Superior parietal	7	L	−29	−63	47	4.64	−0.005
Inferior parietal	40	L	−39	−38	41	4.29	−0.157
MFC	9	L	−13	33	32	4.67	0.063
DLPF	9	L	−37	3	37	5.55	−0.148
VLPF	45	L	−42	21	18	4.64	−0.092
Premotor	6	L	−26	−2	54	4.82	0.029
Moderate pain							
S1	3, 1, 2	R	32	−29	55	11.4	0.234
S2	40	R	41	−29	25	8.54	−0.12
S2	40	L	−53	−19	21	5.95	−0.119
Caudal ACC	24	R	4	3	41	5.64	−0.196
Mid-insula		R	41	−3	20	6.70	−0.066
Anterior insula		L	−28	19	14	5.69	−0.256
Thalamus		R	14	−19	6	4.38	0.095
M1 ventral	4	R	51	0	12	7.71	−0.096
SMA dorsal	6	R	2	−8	67	4.46	−0.191
SMA ventral	6	R	9	−9	52	7.92	0.088
Paracentral lobule	5	R	12	−22	47	5.24	−0.13
Midbrain/PAG		R	8	−23	−5	5.17	−0.032

BA, Brodmann area; DLPF, dorsolateral prefrontral; VLPF, ventrolateral prefrontal; MFC, medial prefrontal cortex; ACC, anterior cingulate cortex.
X, *Y*, and *Z* are Talairach coordinates.
All *t*-values significant at $p < 0.001$, random effects, for single voxel.
All correlations non-significant ($p > 0.10$).

Strong positive correlations were found between individual PCS scores and mild pain-related activations within areas related to the emotional dimension of pain, including the rostral ACC and bilateral insula (Figs. 3 and 4, top panels) as well as in attention-related prefrontal regions (9, 10, and 46). As well, a group of regions involved in motor response/planning were correlated with PCS scores with mild pain, including thalamus, putamen, and premotor cortex. Other regions included inferior parietal cortex, parahippocampus, posterior cingulate, and precuneus.

Conversely, with moderate pain, individual PCS scores showed a strong negative correlation with activity in the DLPF bilaterally (Figs. 3 and 4, bottom panels), which were more dorsal than those prefrontal regions correlated with mild pain. Other regions of the prefrontal cortex (BA 8, 9, and 10), right temporal lobe, posterior parietal (BA 7), amygdala, and lateral S1 also were correlated negatively with PCS scores during moderate pain.

4. Discussion

These data demonstrate that pain-evoked brain activity is related to pain catastrophizing in healthy individuals. During mild pain, activity in brain regions typically associated with the affective, attention, and motor aspects of pain, such as the rostral ACC and insula, was positively related to PCS. With moderate pain, activity within areas associated with top-down pain control, such as the dorsolateral prefrontal cortex, was negatively correlated to individual PCS scores. Therefore, the relationship between pain-evoked activity and PCS is complex and at least partially dependent on pain intensity levels.

4.1. Neural response to sensory-discriminative dimension of pain is conserved

The sensory-discriminative aspects of pain are thought to be subserved by the lateral pain system, which includes the lateral thalamus, S1, and S2 (for review, see Price et al., 2003; Treede et al., 1999). In the present study, we did not find any evidence for a relationship between activity in these areas and an individual's PCS score, nor was there any impact of PCS score on the perception of the sensory qualities of the TENS pain as assessed by MPQ. This finding is in agreement with a previous study of people with fibromyalgia, where catastrophizing did not reflect differences in

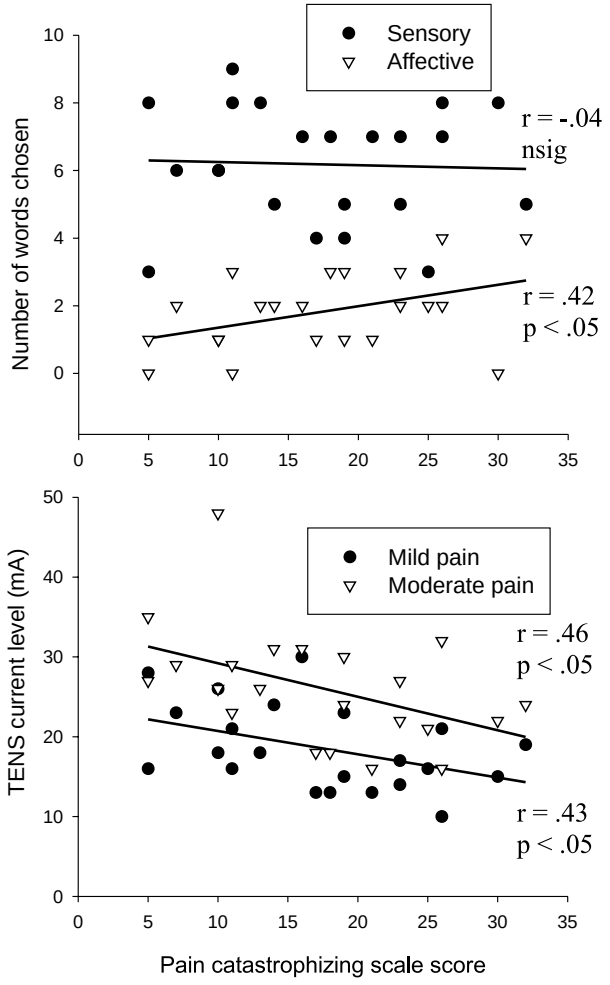

Fig. 2. Scatterplots of the number of words chosen on the McGill Pain Questionnaire short form (MPQ-SF; top graph) completed during moderate pain, and the TENS current level required to achieve a rating of mild or moderate pain (bottom graph) versus pain catastrophizing scale scores. PCS scores are significantly negatively correlated with the level of TENS current and significantly correlated with the number of affective words chosen on the MPQ-SF. See Section 2 for examples of sensory and affective words in the MPQ.

activity in the sensory-discriminative regions including bilateral S1 and S2, and thalamus (Gracely et al., 2004). Therefore, differences in pain responsiveness related to catastrophizing are not directly associated with activity in sensory-discriminative aspects of pain processing.

4.2. Impact of pain catastrophizing on neural activity depends on pain intensity level

Our data revealed differential effects of PCS scores on pain-evoked cortical activity according to the intensity of pain.

A main finding was that during milder pain, PCS scores positively correlated with brain areas – particularly insula and rostral ACC – implicated in the emotional dimension of pain, pain empathy, and attention, as well as interoception (Botvinick et al., 2005; Hofbauer et al., 2001; Jackson et al., 2005; Rainville et al., 1997; Sawamoto et al., 2000; Singer et al., 2004). Furthermore, Wager et al. (2004) showed that activity in the ACC and insula can be reduced with pain placebo. Therefore, our findings also implicate the ACC and insula in pain exacerbation.

The relationship between insula activity (particularly the right anterior region) and PCS scores in mild pain is also interesting in light of this region's proposed role in interoception and "subjective feeling states" (Craig, 2002, 2003; Critchley et al., 2004) as well as attention, awareness, and salience (Downar et al., 2000, 2002). Therefore, insula activity may represent a pain vigilance signal in people deemed "pain catastrophizers".

Our behavioral data add further support to the concept of a pain vigilance factor in pain catastrophizing. First, subjects with higher PCS scores were more sensitive to the TENS stimuli as exemplified by their lower current thresholds for pain. Second, the greater number of affective words (e.g., "sickening", "fearful") used to describe pain in the subjects with higher PCS scores indicates a heightened emotional response to painful stimuli.

Our other main finding was that the more intense (moderate) pain level, PCS score correlated negatively with activity in DLPF and MFC. This was an interesting finding, given that several lines of evidence suggest a role for the DLPF and MFC in pain suppression. For example, PFC microstimulation in rats (Hardy, 1985; Hardy and Haigler, 1985) and transcranial magnetic stimulation in humans with chronic headache (Brighina et al., 2004) reduce nociceptive responses and pain intensity, respectively. The DLPF has also been implicated in top-down control of pain intensity (Lorenz et al., 2003) and in mediating placebo response (Wager et al., 2004). Therefore, our data suggest that individuals, who display catastrophizing behavior, may have difficulty disengaging from intense pain through a lack of top-down control.

4.3. Support for the attention model of pain catastrophizing

Catastrophizing may enhance a person's attention to pain, resulting in difficulty disengaging from pain (see Sullivan et al., 2001; Van Damme et al., 2004), and thus increased attention and awareness to external stimuli or vigilance (Goubert et al., 2004). Our data support this attention model in that the regions that correlated with PCS scores included a number of brain areas involved in pain vigilance, attention to the body or sensory stimuli in general, including prefrontal (DLPF, MFC), premotor, and inferior parietal cortices (Bornhovd et al., 2002; Derbyshire et al., 1997; Downar et al., 2000, 2001, 2002; Ehrsson et al., 2004; Loose et al., 2003).

The discovery that brain activity during mild and moderate pain intensities results in a very different covariance pattern with catastrophizing while activating similar pain-related regions overall was not anticipated,

Table 2
PCS correlations with moderate and mild left-sided pain-evoked BOLD responses

		BA	R/L	*X*	*Y*	*Z*	Volume (mm^3)	*r*-value
Mild pain								
Cingulate	ACC rostral	32	L	−13	45	10	418	0.643
	Posterior	31	R	4	−21	32	118	0.544
	Posterior	31	L	−11	−24	43	278	0.577
Insula	Anterior		R	36	12	7	348	0.538
	Anterior/mid		L	−35	5	3	1120	0.662
	Mid		R	34	2	13	628	0.731
	Posterior		L	−37	−13	3	614	0.712
	Posterior		R	34	−14	4	1310	0.715
	Posterior		L	−52	−31	18	783	0.69
	Posterior		L	−31	−22	23	417	0.661
Prefrontal	DLPF	9	L	−30	39	25	1511	0.669
	DLPF	9	R	19	30	25	466	0.646
	MFC	10	R	17	46	16	386	0.586
	MLPF	46	R	44	31	6	1242	0.609
Premotor	Dorsal	6	L	−7	24	60	170	0.588
	Dorsal	6	L	−16	−19	64	265	0.66
	Ventral	44	R	51	9	13	1024	0.64
Parietal	Inferior	40	R	58	−36	23	1271	0.65
	Inferior	40	R	51	−48	42	70	0.534
	Inferior	43	L	−63	−12	18	128	0.619
	Paracentral lobule	5	R	12	−31	52	69	0.525
	Precuneus	7	L	−17	−62	33	90	0.528
Temporal	Superior	41	R	49	−27	4	448	0.625
	Hippocampal g.		R	25	−21	−6	313	0.564
Subcortical	Putamen		L	−24	−15	6	231	0.602
	Putamen		R	26	16	9	110	0.559
	Thalamus		L	−14	−12	6	536	0.603
	Thalamus		R	16	−13	12	153	0.522
Moderate pain								
Prefrontal	DLPF	8	L	−19	35	47	2700	−0.63
	DLPF	8	R	18	42	42	829	−0.605
	DLPF	8	L	−33	23	49	1137	−0.568
	MFC	10		0	47	13	62	−0.468
	MFC	9	R	1	57	26	86	−0.474
Parietal	Superior	7	L	−25	−47	60	67	−0.516
	S1 (inferior)	3, 1, 2	L	−47	−24	46	329	−0.547
Temporal	Inferior	37	R	36	−59	−2	459	−0.595
	Superior	22	R	56	−45	18	527	−0.707
	Superior	22	R	47	12	−6	145	−0.535
Subcortical	Amygdala		R	20	−5	−9	270	−0.62

These regions were identified in an overall *F* map with $p < 0.05$. Activity in all regions listed had significant partial correlations with PCS, with the contributions of neuroticism and TENS level removed.

but is interesting nonetheless. This finding possibly reflects a balance of attention demands, involving a dynamic attention switch from pain to the cognitive task (see Eccleston and Crombez, 1999, 2005). Different levels of pain intensity (e.g., mild, moderate) may change various features of the overall pain experience (e.g., the threat value of the pain) that compete for attentional resources and covary with catastrophizing scores. Future imaging studies will need to investigate the specific role of fear, threat, and disengagement from pain in the context of catastrophizing.

The attention model of pain catastrophizing also provides a framework for further inspection of our finding during mild and intense pain. Individuals with higher catastrophizing scores seemed to engage more a cortical network implicated in affective, attention, and motor responses. On the other hand, during intense pain these individuals showed little engagement in cortical areas implicated in top-down modulation of pain, indicating a lack of pain control. These findings also provide a neural basis for heightened pain intensity and unpleasantness ratings in people considered to be catastrophizers.

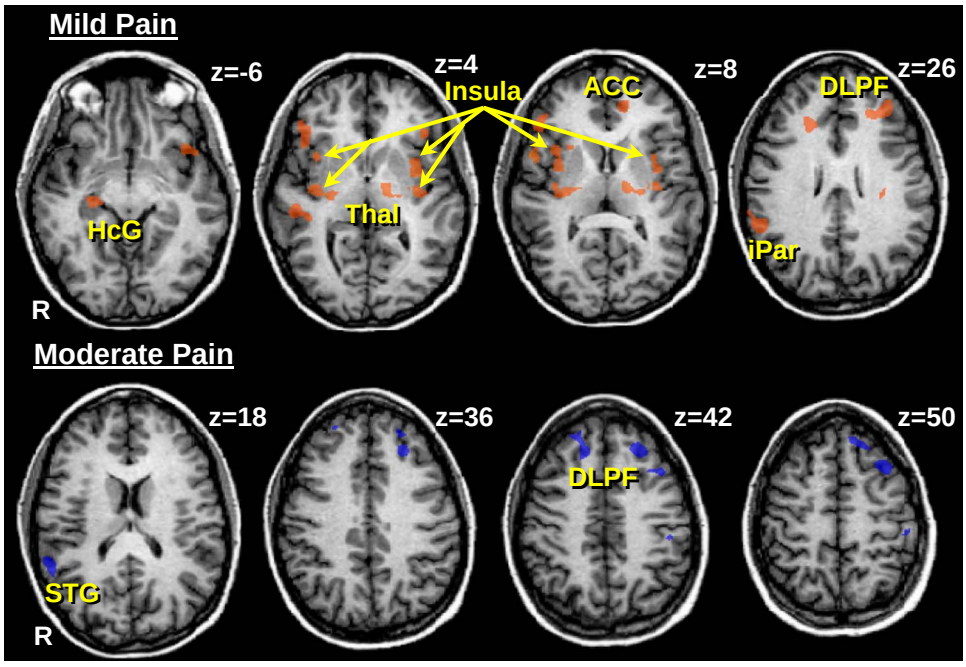

Fig. 3. Regions independently correlated with PCS in mild pain (top) and moderate pain (bottom). Orange indicates the region of positive correlation, blue indicates negative. HcG, hippocampal gyrus; Thal, thalamus; ACC, anterior cingulate cortex; DLPF, dorsolateral prefrontal cortex; R, right side of brain. Talairach *z*-coordinates shown.

Because we collected cognitive task data as part of another study, as a secondary point of interest we were able to test behavioral pain–cognition interactions in relation to pain catastrophizing. From the data in both the fMRI and second sessions, there were no significant correlations between PCS and the difference in reaction time with pain (mild or moderate) versus without pain for each of the task conditions, indicating that reaction times were not modulated by pain as an effect of catastrophizing. Similarly, pain intensity and unpleasantness ratings during the task in the second experimental session did not correlate with PCS scores for any task and there were no significant correlations between PCS scores and the ratings in any condition minus the rating in the tapping control condition. This indicates that catastrophizing did not have an effect on the cognitive modulation of pain ratings.

4.4. Pain catastrophizing as a unique predictor of chronic pain?

The wide range of pain catastrophizing scores in our healthy cohort indicates a variety of responsiveness to pain in the healthy population, and taken together with our imaging results, may have implications for the development and/or persistence of chronic pain.

Catastrophizing has been shown to predict pain levels after a painful procedure (Edwards et al., 2004; Pavlin et al., 2005; Vlaeyen et al., 2004) and can predict health-related quality of life, pain intensity, and disability (Martin et al., 1996; Petrak et al., 2003; Severeijns et al., 2001; Turner et al., 2002). There is also some evidence for the role of catastrophizing in the development of chronic pain (Severeijns et al., 2005). Recent studies have shown that coping strategies may be effective in reducing pain behavior through its effect on reducing catastrophic thinking (Spinhoven et al., 2004; Woby et al., 2005). Thus, reducing negative coping strategies, like catastrophizing, may be an effective way to preempt the development of chronic pain. Our findings support a neural basis for catastrophizing in healthy individuals and suggest potential targets for mediating these changes.

Catastrophizing appears to be a stable trait and is reflected by emotional instability (Thorn et al., 2004). Similarly, neuroticism is a personality trait that reflects negative affect. Several studies have shown a relationship between catastrophizing and neuroticism and pain affect (Goubert et al., 2004; Gracely et al., 2004; Sullivan et al., 2005; Vlaeyen et al., 2004). However, pain catastrophizing can predict pain behavior independent of these other variables (Goubert et al., 2004; Sullivan et al., 1995). Here we showed that while pain catastrophizing, neuroticism, and perceived intensity are all related, catastrophizing independently affects neural activity involved in perceiving pain.

Much of our findings in healthy individuals are in agreement with those of Gracely et al. (2004), who reported the neural correlates of pain catastrophizing in people with chronic fibromyalgia pain. It is thus plau-

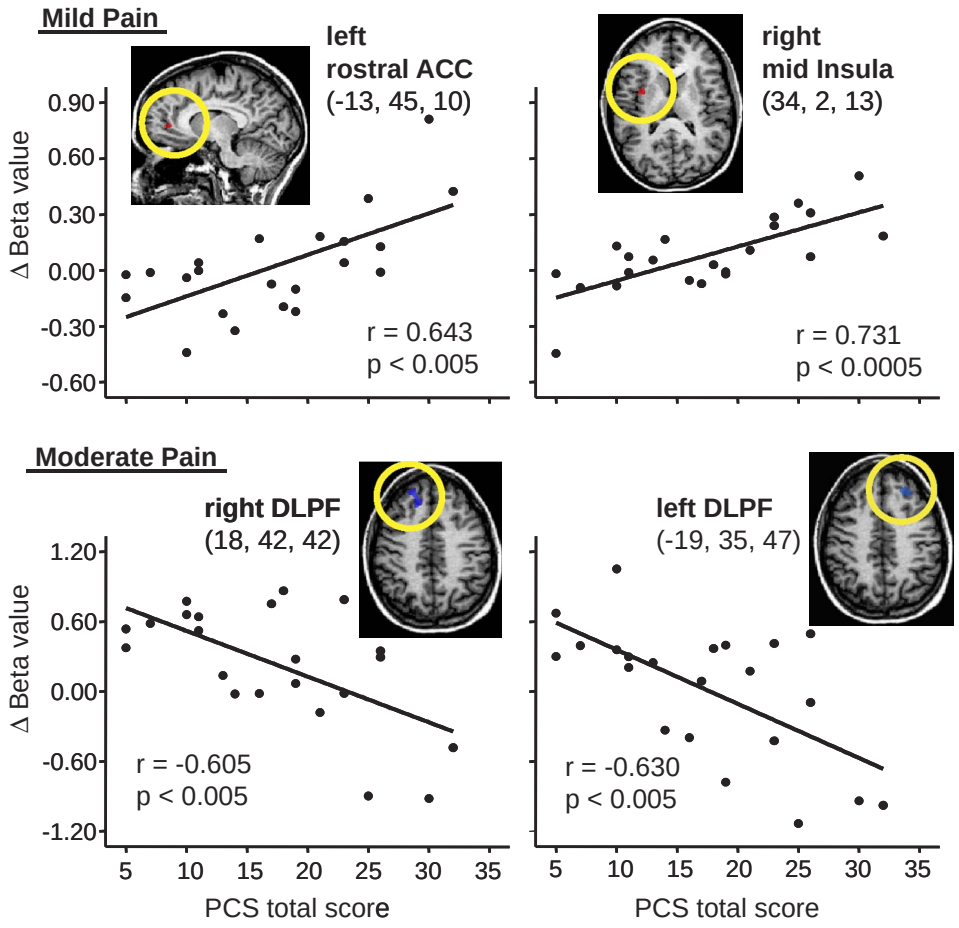

Fig. 4. Representative correlations between pain catastrophizing scale scores (PCS) and brain activity evoked by mild pain (top) and moderate pain (bottom). ACC, anterior cingulate cortex; DLPF, dorsolateral prefrontal cortex. Talairach coordinates shown.

sible that the cortical response to pain is influenced by an individual's level of catastrophizing independent of whether they are in a chronic pain state. This concept has implications in differentiating trait-specific and state-specific relationships of central neural processing of pain and the impact of pre-existing traits on the progression to or persistence of chronic pain.

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