MR. JEUNGCHAN LEE (Orcid ID : 0000-0002-4424-175X)

Article type : Full Length

Running head: PCC encodes pain catastrophizing in fibromyalgia

Title: Encoding of self-referential pain catastrophizing in posterior cingulate cortex in fibromyalgia

Jeungchan Lee,[1] Ekaterina Protsenko,[1] Asimina Lazaridou,[2] Olivia Franceschelli,[2] Dan-Mikael Ellingsen,[1] Ishtiaq Mawla,[1] Kylie Isenburg,[1] Michael P. Berry,[1] Laura Galenkamp,[2] Marco L. Loggia,[1] Ajay D. Wasan,[3] Robert R. Edwards,[2] and Vitaly Napadow[1]

Supported by the National Institutes of Health, National Center for Complementary and Integrative Health (R01-AT007550, R61-AT009306, P01-AT006663), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01-AR064367), and the National Center for Research Resources (P41RR14075, S10RR021110, S10RR023043).

[1] Jeungchan Lee, PhD, Ekaterina Protsenko, BS, BA, Dan-Mikael Ellingsen, PhD, Ishtiaq Mawla, BA, Kylie Isenburg, BS, Michael P. Berry, BS, Marco L. Loggia, PhD, Vitaly Napadow, PhD: Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston MA; [2] Asimina Lazaridiou, PhD, Olivia Franceschelli, BS, Laura Galenkamp, BS, Robert R. Edwards, PhD: Department of Anesthesiology, Harvard Medical School, Brigham & Women's Hospital, Boston MA and Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston MA; [3] Ajay D. Wasan, MD, MSc: Department of Anesthesiology, University of Pittsburg Medical Center, Pittsburgh PA and Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston MA

Drs. Edwards and Napadow contributed equally to this work.

Authors do not have any conflict of interest with regard to the work.

Address correspondence to Jeungchan Lee, PhD, Martinos Center for Biomedical Imaging, 149 Thirteenth Street, Suite 2301, Charlestown, MA 02129. Telephone-number: 1-617-643-0569, E-mail: aeiouphy@nmr.mgh.harvard.edu

ABSTRACT

Objective. Pain catastrophizing is a common feature of chronic pain, including fibromyalgia (FM), and is strongly associated with amplified pain severity and disability. While prior neuroimaging studies have focused on evoked pain response modulation by catastrophizing, the brain mechanisms supporting pain catastrophizing itself are unknown. We designed a functional MRI-based pain catastrophizing task whereby patients with chronic pain engaged in catastrophizing-related cognitions. We hypothesized that catastrophizing about clinical pain would be associated with amplified activation in nodes of the Default Mode Network (DMN), which encode self-referential cognition and show altered functioning in chronic pain.

Methods. During fMRI, fibromyalgia patients (n=31) reflected on how catastrophizing statements (CAT, drawn from the Pain Catastrophizing Scale) impact their typical fibromyalgia pain experience. Response to CAT statements was compared to matched neutral statements (NEU).

Results. During statement reflection, higher fMRI signal during CAT (CAT>NEU) was found in several DMN brain areas, including ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC). Patients' ratings of CAT statement applicability were correlated solely with activity in vPCC, a main DMN hub supporting self-referential cognition ($r=0.38$, $p<0.05$). Clinical pain severity was correlated solely with activity in dPCC, a PCC subregion associated with cognitive control and sensorimotor processing ($r=0.38$, $p<0.05$).

Conclusion. These findings provide evidence that the PCC encodes pain catastrophizing in fibromyalgia, and suggest distinct roles for different PCC subregions. Understanding the brain circuitry encoding pain catastrophizing in FM will prove important in identifying and evaluating the success of interventions targeting negative affect in chronic pain management.

Negative affect plays a key role in the pathophysiology of chronic pain and shapes individual differences in pain treatment outcomes. Pain catastrophizing, in particular, is a pain-specific psychosocial construct comprised of cognitive and emotional processes such as helplessness, pessimism, rumination about pain-related symptoms, and magnification of pain complaints (1). Catastrophizing is also a major contributor to pain severity in fibromyalgia (FM) (2), a chronic functional pain disorder characterized by maladaptive brain plasticity (3). While catastrophizing positively correlates with other measures of negative affect such as anxiety, it also shows a unique and specific influence on pain-related outcomes (2). Overall, higher catastrophizing is a risk factor for long-term pain and for disproportionately-negative pain sequelae (e.g., physical disability) (2,4). Studies in musculoskeletal pain suggest that catastrophizing is the single most important pre-treatment risk factor that impairs the effectiveness of pain-relieving interventions (5). Our own work suggests that catastrophizing amplifies pain sensitivity and brain response and interferes with pain modulation in patients with many chronic pain conditions, including FM (6-8). While trait pain catastrophizing has been shown to shape brain responses to evoked pain stimuli (9), the neural circuitry supporting the pain catastrophizing state itself remains poorly understood. No functional neuroimaging studies have attempted to directly identify the neural underpinnings of chronic pain patients' engagement in the cognitive/emotional processes of catastrophizing.

Several studies have attempted to experimentally induce a pain catastrophizing state, with mixed results. In two separate studies, healthy adults were asked to rehearse catastrophizing self-statements while undergoing cold pressor testing, with no impact on pain sensitivity or tolerance (10,11). However, inducing catastrophizing by experimentally manipulating the perceived threat of pain significantly impacted cold pain responses (12). Furthermore, a study in chronic pain patients found a large reduction in cold pain tolerance when they verbally

recited catastrophizing, relative to positive statements (13). Other studies in patients with chronic musculoskeletal pain have induced a catastrophizing state by asking patients to imagine their pain worsening in the future (14,15). While these studies are limited by lack of randomized design or an active control condition, the cognitive manipulations did enhance sensitivity to experimentally-applied noxious stimuli. Collectively, while prior studies have applied catastrophizing modulation of brain responses to evoked pain or stress in healthy adults (16) and migraine patients (17), no study has applied neuroimaging-based assessment of brain function during actual catastrophizing about clinical pain.

In this study in FM patients, we investigated physiological (heart rate) and functional MRI (fMRI) brain responses to a catastrophizing state induced by visually presenting validated statements from the Pain Catastrophizing Scale (PCS) (18) and asking them to reflect on the degree to which these statements mirrored their experiences with their own recalled, clinical pain. Matched neutral statements were used as controls, and patients rated the applicability of statements to their clinical pain. As multiple studies have linked altered neurophysiology in the brain's default mode network (DMN) to clinical pain severity in fibromyalgia (19,20), and DMN regions are known to encode self-referential cognitive processing (21), we hypothesized that patients would activate DMN regions during catastrophizing, and catastrophizing-specific regions would show an association between fMRI response and ratings of applicability of the catastrophizing statements to patients' clinical pain.

PATIENTS AND METHODS

Patients

Thirty-five female patients meeting the American College of Rheumatology (ACR) criteria for a diagnosis of FM (22) were recruited through Clinical Trials listings (clinicaltrials.partners.org), a Partners Healthcare medical records database, and physician referral. The protocol was approved by the Human Research Committee of Partners Healthcare and Massachusetts General Hospital, and patients provided written informed consent prior to beginning study procedures. This study was registered at clinicaltrials.gov (NCT01345344).

All patients completed phone prescreening to determine study eligibility, and were assessed for the following inclusion criteria: age 18-65; female; meet the Wolfe et al. 2011 research criteria for fibromyalgia for at least one year (22); stable doses of medication prior to entering the study; baseline pain intensity of at least 4/10 on average and pain report for at least 50% of days; able to provide written informed consent; and fluency in English.

Exclusion criteria were: comorbid acute or chronic pain conditions rated more painful than FM; use of stimulant medications for fatigue associated with sleep apnea or shift work; psychiatric disorders with history of psychosis; psychiatric hospitalization within 6 months prior to enrollment; current or recent use of recreational drugs; active suicidal ideation; participation in other therapeutic trials; lower limb vascular surgery or current lower limb vascular dysfunction; pregnancy or nursing; history of significant head injury (e.g., with substantial loss of consciousness); history of anxiety disorders interfering with fMRI procedures (e.g., panic); contraindications to MRI.

Behavioral Visit

All patients completed a behavioral session on a separate day from the MRI scan and were introduced to study procedures, including rating scales and the Pain Catastrophizing Task described below. Additionally, patients completed the following questionnaires: survey of ACR fibromyalgia diagnostic criteria (22), PCS (18), Brief Pain Inventory (BPI) assessing pain severity and interference (23), and Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) assessing several health outcomes (24).

Pain Catastrophizing Task

The Pain Catastrophizing Task (CAT Task, **Figure 1**) consisted of 6 statements drawn from the validated PCS (18) and 6 Velten-type affectively neutral statements taken from a validated set used as a control in prior cognitive/affective research (25,26) and modified to be of similar lexical difficulty and word count to PCS statements (see **Figure 1** for a full list of statements). Only PCS statements containing the word 'pain' were selected, and 2 statements were chosen from each of 3 subscales: helplessness, magnification, and rumination. Statements were presented in a block design, with separate blocks for PCS subscales (CAT) or matched neutral statements (NEU). Each block was presented for 20 seconds (10 seconds/statement, including a 1-second fade-in for smooth visual transition between statements), separated by a 20-second cross-hair fixation rest period. Patients were instructed to read each of statement and reflect on the degree to which they had these thoughts or feelings during a recent, typical day of fibromyalgia pain. No motor responses were required; patients were instructed to simply reflect on their fibromyalgia-related experiences with these thoughts and feelings. This general methodology (i.e., participants read and reflect on affectively-themed statements in order to induce a certain mood) has been used in multiple pain studies, to alter both self-reported mood and pain sensitivity (27). Additionally, each run

contained a single 5-second 'catch trial' (CATCH) in which patients were asked to press any button box button using their left hand to check for alertness and ensure that patients were paying attention to the task.

In order to encourage meaningful reflection and maximize familiarity with the pain catastrophizing task, patients discussed the task with a study investigator prior to each administration. Patients were first introduced to what the task would entail (e.g., "You will be reading some statements on the screen that describe different thoughts and feelings people might have while experiencing pain. We will ask you to think about your experience with these kinds of thoughts during a typical day of fibromyalgia pain.") Patients were then asked to describe a recent typical day of fibromyalgia pain. They were prompted to describe where they felt pain, the quality of sensations (e.g., achy, sharp, tingling), activities that might improve or aggravate pain, and any recent changes in pain.

Following the introduction, patients performed the CAT Task on a laptop (E-Prime 2.0, Psychology Software Tools Inc., PA) and completed a CAT Applicability Questionnaire (CAQ) to assess the degree to which patients endorsed thoughts or feelings related to each statement while reflecting on their pain during the CAT task (5-point Likert scale). Performing this task during the behavioral visit served as task familiarization for the later MRI visit.

MRI Scan Visit

Prior to scanning, FM patients were again asked to discuss a recent typical day of fibromyalgia pain. Patients read the CAT statements on a laptop to familiarize them with the CAT task.

In the MRI scanner, brief task instructions were presented on the screen, and the fMRI CAT Task run was completed twice. The sequence of CAT and NEU blocks was pseudo-randomized (**Figure 1**). After the scan, patients again completed the CAQ and CAT Valence Questionnaire (CVQ), which asked patients to rate how positive or negative they thought each statement was on a visual analog scale (-100: very negative; 0: neutral; +100: very positive). The CVQ was used as a manipulation check to ensure that CAT and NEU statements were perceived as affectively negative and neutral, respectively. State anxiety levels (0: not anxious, 100: extremely anxious) were also asked before and after the two fMRI runs.

Psychophysiological response was also assessed, as phasic heart rate changes have long been used as an objective index of emotional experiences, thereby minimizing self-report biases such as inaccurate recall, response bias, and demand characteristics (28). The electrocardiogram (ECG) was collected during scanning using a MR-compatible system (MP150, Biopac Systems Inc., CA). ECG peaks were annotated using in-house algorithms (MATLAB 8.3) to estimate heart rate (HR) responses to CAT and NEU statements relative to a pre-stimulus baseline. Based on a peri-stimulus plot showing an average time-series of response (**Figure 2A**), average HR was calculated for windows of 4-8 seconds from the onset of each CAT or NEU statement. The averaged HR responses were then normalized with respect to the average HR from a 5-second baseline preceding each block. Differences in

normalized HR response between CAT and NEU blocks were calculated (paired *t*-test, SPSS v.10.0.7, significant at $p<0.05$).

MRI Data Acquisition

MRI data were obtained on a 3.0T Siemens Skyra (Siemens Medical, Erlangen, Germany) equipped with 32-channel head coil at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital. T1-weighted structural images were obtained using a three-dimensional MP-RAGE pulse sequence (TR=2530ms, TE=1.64ms, flip angle=7°, FOV=256×256mm, spatial resolution=1×1×1mm). Functional data (228 volumes/run) were obtained with a simultaneous multi-slice imaging (SMS) pulse sequence for improved spatiotemporal resolution (acceleration factor=5, TR=1250ms, TE=33ms, flip angle=65°, matrix=98×98, voxel size=2×2×2mm, 75 axial slices with no gap) (29).

MRI Data Processing and Analysis

FMRI data processing was carried out using FSL (FMRIB's Software Library, fsl.fmrib.ox.ac.uk), AFNI (Analysis of Functional NeuroImages, afni.nimh.nih.gov/afni), and FREESURFER (https://surfer.nmr.mgh.harvard.edu/fswiki). The first 3 fMRI volumes were removed, and data were then corrected for head motion (FSL-MCFLIRT) and B_0 inhomogeneities (FSL-PRELUDE and -FUGUE), skull stripped (FSL-BET), spatially smoothed (Gaussian kernel, FWHM=5mm), and temporal high-pass filtered (cutoff =80sec) to remove signal drift noise. We used the following head motion exclusion criteria: TR-to-TR displacement and rotation >2mm and 2°, respectively. For co-registration of structural and functional data to standard MNI space (FSL-FNIRT), structural images were aligned to fMRI

data (BBREGISTER).

A first level, within-subject, general linear model (GLM) analysis was performed by modeling CAT and NEU blocks, as well as the CATCH trial block, convolved with the canonical double-gamma hemodynamic response function (FSL-FEAT). The first level parameter estimates and corresponding variance maps from the two fMRI runs were then combined with a second level analysis using a fixed effects model (FSL-FEAT). Resulting parameter estimates and variance maps were then registered to standard space (MNI152) using the FMRIB's Nonlinear Image Registration Tool (FNIRT) and used for group analysis (i.e., CAT and NEU group map, and CAT vs. NEU difference map) using FMRIB's Local Analysis of Mixed Effects (FLAME 1+2, cluster-corrected for multiple comparisons, $Z>2.3$, $p<0.05$).

The CAT vs. NEU difference map was used to identify regions of interest (ROIs), defined as 3-mm diameter spheres centered at the cluster peak voxel. ROI average percent signal change was then used to investigate associations with relevant pain and catastrophizing behavioral outcomes (e.g., PCS, CAQ, BPI, and PROMIS-29).

FREESURFER and CARET (http://sumsdb.wustl.edu/sums/humanpalsmore.do) were used for visualization of results on inflated cerebral and cerebellar surfaces, respectively. As we hypothesized DMN involvement in the brain circuitry encoding catastrophizing, results were visualized on a brain surface with an outline of the publicly available Yeo et al. N=1000 resting connectivity DMN parcellation (30).

RESULTS

Out of thirty-five enrolled fibromyalgia (FM) patients, thirty-one were included in the analyses (age=43.74±11.71 years old, mean±SD) (26 Caucasian, 2 African-American, 1 Asian, 1 Cape Verdean, and 1 non-responder). Four FM patients were excluded from analyses due to structural brain abnormalities (n=2), inability to comply with MRI safety requirements (n=1), and falling asleep during fMRI (n=1, failed to respond to 'catch trial' and retrospectively confirmed by patient).

Clinical Measures

FM patients reported moderate to high PCS (21.03±12.92), BPI (severity=4.74±1.87, interference=5.13±2.41), and PROMIS-29 scores (physical function=39.89±6.96, anxiety=56.73±8.13, depression=53.68±8.97, sleep disturbance=58.73±8.13, satisfaction with participation in social roles=46.96±13.91) at the initial behavioral visit.

After two CAT Task fMRI runs, patients reported higher CAQ (statement applicability) scores for CAT compared to NEU blocks (CAQ_{CAT}=6.90±4.64, CAQ_{NEU}=2.03±2.93, p<0.0001 for the CAT-NEU comparison). CVQ scores demonstrated that CAT statements were indeed perceived as affectively negative (CVQ_{CAT}=-57.86±37.68), while neutral statements were not perceived as having negative valence (CVQ_{NEU}=7.88±19.00, p<0.00001 for the CAT-NEU comparison) (**Table 1**). State anxiety levels showed no significant difference between before and after two CAT task fMRI runs (pre=21.25±18.54, post=21.32±20.02, N=28, p=0.93).

PCS scores correlated positively with CAQ_{CAT} scores (r=0.81, p<0.0001), BPI (interference: r=0.45, p<0.05), and PROMIS-29 subscales (anxiety: r=0.73, p<0.0001; depression: r=0.66, p<0.0001). Furthermore, CAQ_{CAT} scores positively correlated with BPI (interference: r=0.52, p<0.01) and PROMIS-29 subscales (anxiety: r=0.69, p<0.0001; depression: r=0.60,

p<0.0001; sleep disturbance: r=0.39, p<0.05; satisfaction with participation in social roles: r=-0.37, p<0.05).

Brain and psychophysiological responses during catastrophizing

Data from all 31 FM patients were available for fMRI analysis, as all patients passed head motion exclusion criteria. To assess psychophysiological arousal, we quantified HR responses and found greater HR increase during CAT (0.96±0.24BPM), compared to NEU (0.49±0.16) statements (p=0.03, **Figure 2B**).

Group maps demonstrated similar brain responses to CAT and NEU statements in visual information processing areas (e.g., occipital cortex) and lexical processing areas (e.g., ventrolateral prefrontal cortex and posterior superior temporal sulcus) (**Supplementary Figure 1**).

The CAT-NEU difference map revealed a significant positive contrast in left ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC, respectively), precuneus (PC), left ventrolateral prefrontal cortex (vlPFC), left angular gyrus/inferior parietal lobule (IPL), left medial prefrontal cortex (mPFC), and right cerebellum. Most of the CAT-NEU clusters were within the boundaries of the default mode network (DMN), as outlined in yellow (**Figure 3**) by DMN parcellation (30). The CAT-NEU difference map also showed a significantly negative contrast in bilateral parietal lobule, left medial temporal lobe (MTL), and bilateral inferior temporal gyrus (ITG, temporo-occipital part) (**Figure 3, Table 2**). Notably, as also evidenced by the difference map group bar plots (**Figure 3**) and group maps (**Supplementary Figure 1**), regions such as PCC showed activation for CAT and deactivation for NEU, while for other DMN regions such as mPFC, there was reduced

deactivation for CAT compared to NEU, which also presented as a positive CAT-NEU contrast.

Association between CAT-specific brain responses and clinical/psychometric measures

We found that vPCC activation during CAT was positively correlated with CAQ_{CAT} score (total: r=0.38, p<0.05), while dPCC activation during CAT was positively correlated with BPI subscales (severity: r=0.38, p<0.05; interference: r=0.38, p<0.05) (**Figure 4**). No other brain region ROI showed significant correlation with these clinical/psychometric measures (e.g., vPCC vs. BPI severity: r=0.11, p=0.57; vPCC vs. PROMIS-29 anxiety: r=0.20, p=0.30; vPCC vs. PROMIS-29 depression: r=0.17, p=0.37; dPCC vs. CAQ_{CAT}: r=0.28, p=0.13).

DISCUSSION

Pain catastrophizing plays a substantial role in the pathophysiology of fibromyalgia: here we investigated the neural circuitry supporting pain catastrophizing in FM. Patients reflected on their experiences with pain-referential catastrophizing statements during a recent episode of fibromyalgia pain. These procedures allowed patients prone to catastrophizing to engage in such ruminative cognitions, while fMRI tracked brain activity. These FM patients reported, on average, high PCS scores, with relatively high inter-patient variability. Compared to neutral statements, reflection on pain catastrophizing statements was encoded by activation of ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC), in addition to other, mainly default mode network (DMN), brain regions. Importantly, vPCC and dPCC were the only brain areas that showed a positive correlation between catastrophizing-related activation (CAT-NEU) and clinical measures of catastrophizing and FM pain. Specifically, patients who found the catastrophizing statements most applicable

while reflecting on their pain also showed greater vPCC activation. In addition the severity and interference of FM clinical pain (i.e., BPI score) was associated with dPCC activation. Taken together, these findings suggest that posterior cingulate cortex encodes pain catastrophizing in fibromyalgia.

While prior neuroimaging studies have explored how catastrophizing influences brain response to evoked pain stimuli, our study directly investigated the brain activity supporting catastrophizing cognitions in FM patients. The striking involvement of multiple DMN regions in pain catastrophizing is consistent with previous research. For instance, induced negative mood (using depressing music and visual lexical cues) activates mPFC, and increases PCC response to evoked pain stimuli in healthy adults (16). In fact, prior research has consistently shown reduced DMN deactivation in response to a range of externally-focused tasks in chronic pain patients (31,32). Our results suggest that reduced PCC deactivation in chronic pain patients may be due to ongoing catastrophizing-associated activity in this brain area while processing pain-related external stimuli.

We found not only greater brain activation in vPCC in response to catastrophizing about FM pain, but also a significant association between vPCC activity and CAQ score. PCS score was positively correlated with CAQ score; hence, patients who reported greater *trait* catastrophizing also reported greater applicability and endorsement of catastrophizing statements to their own pain during recall. In turn, greater applicability of catastrophizing statements was associated with greater vPCC activation, closely linking this subregion of the posterior cingulate cortex to the catastrophizing state. The vPCC is a cardinal node of the DMN (21), and has been strongly linked with self-referential cognition, attentional focus, and arousal (33). The vPCC has been differentiated from the more anterior dPCC subregion based

on cytoarchitecture (34) and connectivity to canonical brain networks. Specifically, while both PCC subregions show strong connectivity to the DMN, the dPCC also shows greater connectivity to dorsal attention, central executive, and even salience networks (35), suggesting that dPCC also plays a broader role in attentional focus, modulating dynamic interactions between the DMN and heteromodal cognitive control and attention networks. In contrast, the vPCC shows greater linkage to medial temporal lobe regions of the DMN (e.g., hippocampus), and may thus play a greater role in self-referential cognition and autobiographical memory (33).

Interestingly, previous neuroimaging studies have linked PCC neurophysiology with trait pain catastrophizing, as assessed by the PCS questionnaire. For instance, Fayed et al. used Magnetic Resonance Spectroscopy (H-MRS) and found increased glutamate and glutamine (Glx) levels in FM for a PCC subregion consistent with vPCC, suggesting increased excitatory neurotransmission in this area (36). Importantly, greater Glx levels were positively correlated with greater trait PCS scores. Another study noted that increased connectivity between vPCC and mPFC in chronic pain patients was strongly associated with trait PCS rumination about pain (37). Similarly, fMRI data collected during a self-appraisal task showed not only greater activation in PCC, IPL, and mPFC during the self-appraisal condition but also greater PCC activation in depressed individuals compared to healthy controls (38). These findings suggest that the trait tendency for pain-associated rumination and catastrophizing leads to increased vPCC connectivity to other DMN areas, and stems from, or even induces, increased excitatory neurotransmission in the vPCC subregion of the posterior cingulate. Coupled with our results, we suggest that such altered vPCC neurophysiology may be maintained by ongoing vPCC activity while engaged in self-referential rumination – i.e. the pain catastrophizing *state*. Interestingly, while PCS and CAQ

scores were highly correlated with each other (r=0.81) in our study, PCS score was not associated with vPCC activation in response to our CAT task (r=0.20, p=0.27), suggesting that greater activation (compared to neutral statements) is more of a state phenomenon, while altered connectivity and Glx levels for vPCC may reflect more stable trait catastrophizing. Additional support for a phasic response is provided by the lack of post-run increase in general anxiety levels, suggesting limited carryover and independent cognitive/affective processing during distinct statement blocks. Such independent processing allows for accurate GLM modeling with fMRI block design, as patients likely engaged in catastrophizing during the CAT blocks (as supported by elevated psychophysiological response), but not into subsequent blocks or post-run ratings.

We also found that dPCC activity, which was increased during CAT compared to NEU, was positively correlated with FM pain severity and interference scores. This association suggests a differential function of dPCC, compared to vPCC, during catastrophizing. PCC subregions consistent with the dPCC cluster we identified were functionally connected to not only other DMN regions, but also regions of central executive and even sensorimotor networks (33). Similarly, Vogt et al. have also shown heterogeneity of PCC based on cytoarchitecture and resting glucose metabolism of PCC subregions, suggesting that vPCC plays an important role in self-monitoring, while dPCC interacts more with cingulate motor area and is related to motor and nociceptive information processing (34). Thus, dPCC is a key DMN node that may facilitate communication with other intrinsic brain networks (e.g. sensorimotor and higher cognitive processing networks), and is thus well positioned to link self-referential attentional focus with clinical pain perception. This hypothesis is supported by our results demonstrating that greater clinical pain perception in FM patients was specifically associated with greater dPCC activation during catastrophizing. In fact, dPCC may prove to be a future target for

pain modulation, as reducing activity during catastrophizing may be critical to break the linkage between engaging in negative, ruminative thought and increased clinical pain perception in chronic pain patients. Several groups have stressed the importance of reducing catastrophizing to better manage FM pain (39-43), and dPCC response may be a viable surrogate and even predictive brain imaging marker to evaluate the success of individualized interventions that target catastrophizing, such as cognitive behavioral therapy (39). Furthermore, differential dorsal and ventral PCC roles can also aid self-regulation fMRI neurofeedback design for FM pain, as several previous studies have shown that PCC can be modulated using real-time neurofeedback by focusing on the cognitive process of self-referential experience (to increase fMRI activity, (44)) and meditation (to decrease activity, (45)).

Overall, the brain regions activated during the catastrophizing task support both cognitive and affective experience, as PCC has commonly been linked with self-referential cognition, while mPFC is activated by negative mood induction (16) and its connectivity with PCC is increased in conjunction with rumination about chronic pain (37). Increased IPL activities has also been reported to painful pressure stimulation in FM patients (9), and also been shown to be involved in emotion processing (46). Cerebellum (Crus I and II, posterior cerebellum, CAT>NEU) activity and connectivity (47) has also been related to the cognitive (e.g., language and executive) function (48). Collectively, our findings are likely related to both cognitive and affective aspects of pain catastrophizing. Furthermore, significantly greater psychophysiological (HR increases) response during CAT compared to NEU blocks suggests greater cognitive/affective engagement by patients toward the catastrophizing task (49).

Limitations to our study should also be noted. For instance, the neutral statements chosen as a control in this experiment were not explicitly self-referential, as opposed to the pain catastrophizing statements. While this difference likely played a role in DMN targeting in our fMRI results, the association between activity in specific DMN subregions (i.e., PCC) and both CAQ and pain severity demonstrates that DMN regions did not simply encode the self-referential aspects of the CAT statements but were also linked with FM patients' catastrophizing and clinical pain levels. Moreover, we were not able to use self-referential control "neutral" statements, as any self-referential statements would be susceptible to negatively-valenced interpretation by patients prone to catastrophizing. Another limitation was that we did not have direct measures of patients' re-experienced pain catastrophizing during CAT blocks, as we did not want to encroach on their self-referential rumination with thought probe ratings. We instead used cardioautonomic psychophysiological response as an objective proxy for cognitive/emotional engagement in the task. Additionally, our design did not allow for an explicit separation of pain catastrophizing from general negative affect, as these constructs are known to be closely linked. Finally, while our brain-behavioral correlation analysis approach risked false positive results by not controlling for multiple comparisons, we note that false negative error is an important consideration in novel studies for specific areas of research (50). Hence, future studies will attempt to independently replicate these findings, specifying *a priori* ROI-based hypotheses and including additional control conditions.

In conclusion, our study found that pain catastrophizing led FM patients to activate ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC). The extent to which FM patients catastrophized while reflecting on their pain was specifically associated with vPCC activation during the task. In contrast, dPCC activation during the task was

specifically associated with the severity and interference of clinical pain. The present work enhances the clinical relevance of prior studies that attempted to induce the experience of catastrophizing; most previous designs involved healthy young adults who were asked to rehearse catastrophizing self-statements during the experience of an externally-applied noxious stimulus (10,11,13). In contrast, we recruited patients experiencing a distressing chronic pain condition and imaged their brain during engagement in catastrophizing about past episodes of their clinical pain. These findings provide evidence that posterior cingulate cortex may support pain catastrophizing in fibromyalgia, and suggest distinct roles for different PCC subregions. Understanding the brain circuitry encoding pain catastrophizing in FM is an important step to identifying interventions targeting negative affect for this highly susceptible patient population.

REFERENCES

1. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001;17:52-64.

2. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216-24.

3. Clauw DJ. Fibromyalgia: A clinical review. Jama 2014;311:1547-55.

4. Khan RS, Ahmed K, Blakeway E, Skapinakis P, Nihoyannopoulos L, Macleod K, et al. Catastrophizing: A predictive factor for postoperative pain. Am J Surg 2011;201:122-31.

5. Karels CH, Bierma-Zeinstra SM, Burdorf A, Verhagen AP, Nauta AP, Koes BW. Social and psychological factors influenced the course of arm, neck and shoulder complaints. J Clin Epidemiol 2007;60:839-48.

6. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. J Pain 2011;12:953-63.

7. Kim J, Loggia ML, Cahalan CM, Harris RE, Beissner F, Garcia RG, et al. The somatosensory link in fibromyalgia: Functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. Arthritis Rheumatol 2015;67:1395-405.

8. Loggia ML, Berna C, Kim J, Cahalan CM, Martel MO, Gollub RL, et al. The lateral prefrontal cortex mediates the hyperalgesic effects of negative cognitions in chronic pain patients. J Pain 2015;16:692-9.

9. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835-43.

10. Bialosky JE, Hirsh AT, Robinson ME, George SZ. Manipulation of pain catastrophizing: An experimental study of healthy participants. J Pain Res 2008;1:35-41.

11. Severeijns R, van den Hout MA, Vlaeyen JW. The causal status of pain catastrophizing: An experimental test with healthy participants. Eur J Pain 2005;9:257-65.

12. Wang Y, Jackson T, Cai L. Causal effects of threat and challenge appraisals on coping and pain perception. Eur J Pain 2016;20:1111-20.

13. Roditi D, Robinson ME, Litwins N. Effects of coping statements on experimental pain in chronic pain patients. J Pain Res 2009;2:109-16.

14. Taub CJ, Sturgeon JA, Johnson KA, Mackey SC, Darnall BD. Effects of a pain catastrophizing induction on sensory testing in women with chronic low back pain: A pilot study. Pain Res Manag 2017;2017:7892494.

15. Darnall BD, Aickin M, Zwickey H. Pilot study of inflammatory responses following a negative imaginal focus in persons with chronic pain: Analysis by sex/gender. Gend Med 2010;7:247-60.

16. Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biol Psychiatry 2010;67:1083-90.

17. Goli Z, Asghari A, Moradi A. Effects of mood induction on the pain responses in patients with migraine and the role of pain catastrophizing. Clin Psychol Psychother 2016;23:66-76.

18. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation. Psychological assessment 1995;7:524.

19. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum 2012;64:2398-403.

20. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010;62:2545-55.

21. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: Anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1-38.

22. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The american college of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600-10.

23. Cleeland CS, Ryan KM. Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singapore 1994;23:129-38.

24. Katz P, Pedro S, Michaud K. Performance of the patient-reported outcomes measurement information system 29-item profile in rheumatoid arthritis, osteoarthritis, fibromyalgia, and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2017;69:1312-21.

25. Ben-David BM, van Lieshout PH, Leszcz T. A resource of validated affective and neutral sentences to assess identification of emotion in spoken language after a brain injury. Brain Inj 2011;25:206-20.

26. Velten E, Jr. A laboratory task for induction of mood states. Behav Res Ther 1968;6:473-82.

27. Zelman DC, Howland EW, Nichols SN, Cleeland CS. The effects of induced mood on laboratory pain. Pain 1991;46:105-11.

28. Balzarotti S, Biassoni F, Colombo B, Ciceri MR. Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. Biol Psychol 2017;130:54-66.

29. Cauley SF, Polimeni JR, Bhat H, Wald LL, Setsompop K. Interslice leakage artifact reduction technique for simultaneous multislice acquisitions. Magn Reson Med 2014;72:93-102.

30. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:1125-65.

31. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: Chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008;28:1398-403.

32. Weissman-Fogel I, Moayedi M, Tenenbaum HC, Goldberg MB, Freeman BV, Davis KD. Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. Pain 2011;152:384-96.

33. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain 2014;137:12-32.

34. Vogt BA, Vogt L, Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. Neuroimage 2006;29:452-66.

35. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: Distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J Neurosci 2011;31:3217-24.

36. Fayed N, Andres E, Rojas G, Moreno S, Serrano-Blanco A, Roca M, et al. Brain dysfunction in fibromyalgia and somatization disorder using proton magnetic resonance spectroscopy: A controlled study. Acta Psychiatr Scand 2012;126:115-25.

37. Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, et al. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. J Neurosci 2014;34:3969-75.

38. Davey CG, Breakspear M, Pujol J, Harrison BJ. A brain model of disturbed self-appraisal in depression. Am J Psychiatry 2017;174:895-903.

39. Lazaridou A, Kim J, Cahalan CM, Loggia ML, Franceschelli O, Berna C, et al. Effects of cognitive-behavioral therapy (cbt) on brain connectivity supporting catastrophizing in fibromyalgia. Clin J Pain 2017;33:215-21.

40. Edwards RR, Bingham CO, 3rd, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis Rheum 2006;55:325-32.

41. Burns JW, Day MA, Thorn BE. Is reduction in pain catastrophizing a therapeutic mechanism specific to cognitive-behavioral therapy for chronic pain? Transl Behav Med 2012;2:22-9.

42. Mansell G, Kamper SJ, Kent P. Why and how back pain interventions work: What can we do to find out? Best Pract Res Clin Rheumatol 2013;27:685-97.

43. Tran ST, Guite JW, Pantaleao A, Pfeiffer M, Myer GD, Sil S, et al. Preliminary outcomes of a cross-site cognitive-behavioral and neuromuscular integrative training intervention for juvenile fibromyalgia. Arthritis Care Res (Hoboken) 2017;69:413-20.

44. Brewer JA, Garrison KA, Whitfield-Gabrieli S. What about the "self" is processed in the posterior cingulate cortex? Front Hum Neurosci 2013;7:647.

45. Garrison KA, Scheinost D, Worhunsky PD, Elwafi HM, Thornhill TAt, Thompson E, et al. Real-time fmri links subjective experience with brain activity during focused attention. Neuroimage 2013;81:110-8.

46. Engelen T, de Graaf TA, Sack AT, de Gelder B. A causal role for inferior parietal lobule in emotion body perception. Cortex 2015;73:195-202.

47. Krienen FM, Buckner RL. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 2009;19:2485-97.

48. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. Neuroimage 2009;44:489-501.

49. Weis PP, Herbert C. Bodily reactions to emotional words referring to own versus other people's emotions. Front Psychol 2017;8:1277.

50. Lee EC, Whitehead AL, Jacques RM, Julious SA. The statistical interpretation of pilot trials: Should significance thresholds be reconsidered? BMC Med Res Methodol 2014;14:41.

FIGURE LEGENDS

Figure 1: Pain catastrophizing task. A, Statements were presented in a block design, with each block corresponding to either one of the 'Pain Catastrophizing Scale' subscales (CAT) or matched neutral statements (NEU), and catch trial as a check for alertness (CATCH). B, Entire CAT and NEU statements, instruction for CATCH, and cross-hair fixation for rest (REST) were listed.

Figure 2: Heart Rate (HR) responses to CAT and NEU statements. A, Average HR time-series data show different patterns during CAT and NEU statement blocks. B, HR increase to CAT was significantly greater than that of the increase to NEU. CAT=Catastrophizing statements, NEU=Neutral statements, BPM=Beat per Minute. Bar plot shows mean±SEM. *p<0.05, **p<0.01, ***p<0.001.

Figure 3: Brain responses during catastrophizing. A, Most of the positive contrast (CAT>NEU) clusters in cerebral cortex including ventral and dorsal posterior cingulate cortex (vPCC and dPCC), medial prefrontal cortex (mPFC), inferior parietal lobule (IPL) were within the boundary of 'Default Mode Network (DMN), as defined by N=1000 resting-state fMRI parcellation by Yeo et al. (30)' (*yellow outline*). B, Right cerebellum demonstrated significant positive contrast between CAT and NEU. CAT=Catastrophizing statements, NEU=Neutral statements, dPCC=dorsal posterior cingulate cortex, vPCC=ventral posterior cingulate cortex, mPFC=medial prefrontal cortex, AnG=angular gyrus, IPL=inferior parietal lobule, L=left hemisphere, R=right hemisphere. Bar plots show mean±SEM.

Figure 4: The regions from the CAT-NEU difference map demonstrating an association with clinical/psychometric measures were: 1) dPCC response to CAT was positively correlated

with clinical fibromyalgia pain severity (i.e., BPI severity), and 2) vPCC response was positively correlated with ratings of catastrophizing applicability (i.e., CAQ score). CAT=Catastrophizing statements, NEU=Neutral statements, dPCC=dorsal posterior cingulate cortex, vPCC=ventral posterior cortex, BPI=Brief Pain Inventory, CAQ=CAT Applicability Questionnaire.

Supplementary Figure 1: Brain responses to CAT (A) and NEU (B) statements, and CATCH (C). The group map for CAT showed PCC activation, while for NEU, PCC deactivation is clearly noted. For both CAT and NEU statements, standard regions for lexical (vlPFC, pSTS) and visual (occipital cortex, lateral geniculate nucleus) processing were activated. Increased brain responses to CATCH were observed in visual and sensory/motor processing area (S1/M1, particularly in the right hemisphere contralateral to the button press hand), salience (INS, aMCC) and attention networks (lateral prefrontal cortex, SPL, STG). CAT=Catastrophizing statements, NEU=Neutral statements, dPCC=dorsal posterior cingulate cortex, vPCC=ventral posterior cingulate cortex, PCG=precentral gyrus, SMA=supplement motor area, mPFC=medial prefrontal cortex, vlPFC=ventrolateral prefrontal cortex, pSTS=posterior superior temporal sulcus, AnG=angular gyrus, IPL=inferior parietal lobule, S1=primary somatosensory cortex, M1=primary motor cortex, INS=insular cortex, aMCC=anterior middle cingulate cortex, SPL=superior parietal lobule, MFG=middle frontal gyrus, STG=superior temporal gyrus, L=left hemisphere, R=right hemisphere.

TABLE 1. Demographics and clinical/psychometric measures*

Demographics	**FM (N=31)**
Age (years old)	43.74±11.71
Clinical Pain Measures	
Duration (years, since symptom onset)	7.65±7.05
Brief Pain Inventory (BPI)	
Severity (0-10)	4.74±1.87
Interference (0-10)	5.13±2.41
PROMIS-29 (normalized *t*-scores)	
Physical Function	39.89±6.96
Anxiety	56.73±8.13
Depression	53.68±8.97
Sleep Disturbance	58.73±8.13
Satisfaction with Participation in Social Roles	46.96±13.91
Catastrophizing-associated Measures	
Pain Catastrophizing Survey (PCS, 0-52)	21.03±12.92
CAT Task-recalled Pain Experience	
Pain Intensity (0-100)	56.20±19.00; N=25
Pain Unpleasantness (0-100)	59.31±20.24; N=26
CAT Applicability Questionnaire (0-20)	
Total CAT (CAQ_{CAT})	6.90±4.64
Total NEU (CAQ_{NEU})	2.03±2.93
P-value (CAQ_{CAT} vs. CAQ_{NEU})	< 0.0001
CAT Valence Questionnaire (-100: negative, +100: positive)	
Total CAT (CVQ_{CAT})	-57.86±37.68
Total NEU (CVQ_{NEU})	7.88±19.00
P-value (CVQ_{CAT} vs. CVQ_{NEU})	< 0.00001

* Data are shown as mean±SD. FM=Fibromyalgia, CAQ: Catastrophizing Applicability Questionnaire, which assessed the extent to which patients had thoughts or feelings described on statements while reflecting on their pain during the CAT task. CVQ: Catastrophizing Valence Questionnaire, which assessed patients' ratings of how positive or negative each statement was on a visual analog scale. CAT=Catastrophizing statements, NEU=Neutral statements.

TABLE 2. Brain response during catastrophizing fMRI task*

	Side	Size (mm^3)	Location (MNI, mm)			Z-score	Z-score	
			X	Y	Z		CAT	NEU
CAT > NEU								
cerebellum	R	21448	32	-74	-38	5.26	1.79±1.51	0.04±1.22
dPCC	L	2576	-2	-20	36	5.10	0.64±1.66	-1.16±1.93
vPCC	L	6848	-4	-42	26	4.95	1.32±1.83	-0.90±2.32
PC	L	6848	-4	-72	38	4.65	1.34±2.36	-0.45±2.90
angular gyrus	L	10512	-44	-62	36	4.43	0.77±1.79	-0.60±2.05
preSMA/SMA	L	6440	-14	20	62	4.02	1.33±1.55	0.27±1.78
vlPFC	L	1984	-50	22	0	4.27	2.78±2.06	1.38±1.68
dlPFC	L	6240	-20	56	28	4.00	1.03±1.68	-0.39±1.56
mPFC	L	6240	-12	54	10	3.75	-0.02±1.33	-1.17±1.60
CAT < NEU								
MTL	L	30248	-34	-30	-20	-5.21	-0.96±1.37	1.26±2.06
IPL	L	21128	-28	-70	36	-4.99	2.59±2.94	4.86±3.32
	R	14576	42	-76	26	-4.05	-1.60±2.55	-0.55±2.29
SPL	L	21128	-16	-56	58	-3.75	-0.69±1.99	0.32±2.08
	R	14576	12	-60	58	-3.87	-1.02±2.44	0.31±2.38
ITG	L	30248	-46	-54	-14	-5.73	1.80±2.57	3.87±3.05
	R	6312	60	-60	-14	-3.80	-0.74±1.25	0.37±1.45
premotor area	L	7504	-31	-4	66	-3.48	-0.07±1.31	0.66±1.36
	R	6288	28	14	58	-4.02	-1.23±1.89	0.04±1.94
M1	L	7504	-42	-10	46	-3.48	0.68±1.39	1.47±1.78

* Data are shown as mean±SD. CAT=catastrophizing statements, NEU=neutral statements; L=Left hemisphere, R=Right hemisphere; dPCC=dorsal posterior cingulate cortex, vPCC=ventral posterior cingulate cortex, PC=precuneus, SMA=supplementary motor area, vlPFC=ventrolateral prefrontal cortex, dlPFC=dorsolateral prefrontal cortex, mPFC=medial prefrontal cortex, MTL=medial temporal lobule, IPL=inferior parietal lobule, SPL=superior parietal lobule, ITG=inferior temporal gyrus, M1=primary motor cortex.