ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 8, August 2018, pp 1308–1318
DOI 10.1002/art.40507

Encoding of Self-Referential Pain Catastrophizing in the Posterior Cingulate Cortex in Fibromyalgia

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Objective. **Pain catastrophizing is a common feature of chronic pain, including fibromyalgia (FM), and is strongly associated with amplified pain severity and disability. While previous neuroimaging studies have focused on evoked pain response modulation by catastrophizing, the brain mechanisms supporting pain catastrophizing itself are unknown. We designed a functional magnetic resonance imaging (fMRI)–based pain catastrophizing task whereby patients with chronic pain engaged in catastrophizing-related cognitions. We undertook this study to test our hypothesis 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, 31 FM patients reflected on how catastrophizing (CAT) statements (drawn from the Pain Catastrophizing Scale) impact their typical FM pain experience. Response to CAT statements was compared to response to matched neutral (NEU) statements.**

Results. **During statement reflection, higher fMRI signal during CAT statements than during NEU statements was found in several DMN brain areas, including the ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC, respectively). Patients' ratings of CAT statement applicability were correlated solely with activity in the vPCC, a main DMN hub supporting self-referential cognition ($r = 0.38$, $P < 0.05$). Clinical pain severity was correlated solely with activity in the 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 FM and suggest distinct roles for different PCC subregions. Understanding the brain circuitry encoding pain catastrophizing in FM will prove to be 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 comprising 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 correlates positively 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 of musculoskeletal pain suggest that catastrophizing is the single most important pretreatment risk factor that impairs the effectiveness of pain-relieving interventions (5). Our own work suggests that

Clinical Trials.gov identifier: NCT01345344.

Supported by the NIH (National Center for Complementary and Integrative Health grants R01-AT-007550, R61-AT-009306, and P01-AT-006663, National Institute of Arthritis and Musculoskeletal and Skin Diseases grant R01-AR-064367, and National Center for Research Resources grants P41-RR-14075, S10-RR-021110, and S10-RR-023043).

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Submitted for publication November 3, 2017; accepted in revised form March 20, 2018.

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 2 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 the lack of a 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 physiologic (heart rate [HR]) and functional magnetic resonance imaging (fMRI) brain responses to a catastrophizing state induced by visually presenting validated statements from the Pain Catastrophizing Scale (PCS) (18) and asking the patients 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 FM (19,20), and since DMN regions are known to encode self-referential cognitive processing (21), we hypothesized that patients would activate DMN regions during catastrophizing, and that 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.

All patients completed telephone prescreening to determine their eligibility for the study, and all patients were assessed for the following inclusion criteria: be ages 18–65 years and female; meet the ACR diagnostic criteria for FM for at least 1 year (22); receive stable doses of medication prior to entering the study; have baseline pain intensity of at least 4 of 10 on average and report pain for at least 50% of days; be able to provide written informed consent; and be fluent 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; pregnant 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); and 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: PCS (18); Brief Pain Inventory (BPI) (23), to assess pain severity and interference; and Patient-Reported Outcomes Measurement Information System 29-Item Profile (PROMIS-29), to assess several health outcomes (24).

Pain catastrophizing (CAT) task. The pain 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 have lexical difficulty and word count similar 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 statements) and matched neutral (NEU) statements. Each statement 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 statement and reflect on the degree to which they had these thoughts or feelings during a recent typical day of FM pain. No motor responses were required; patients were instructed to simply reflect on their FM-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

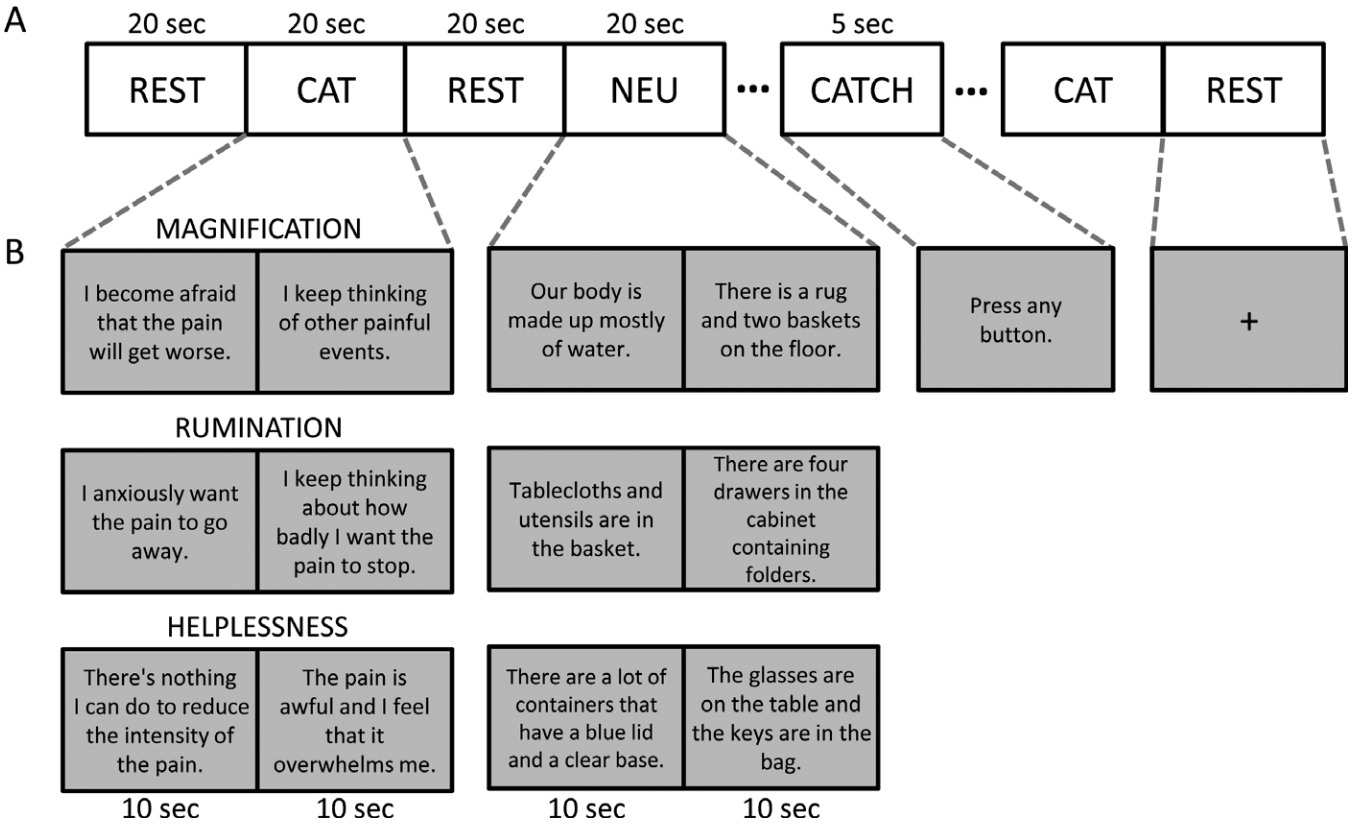

Figure 1. Pain catastrophizing (CAT) task. **A,** Statements were presented in a block design, with each block corresponding to either one of the Pain Catastrophizing Scale subscales (CAT statements) or matched neutral (NEU) statements, and with a catch trial (CATCH) as a check for alertness. **B,**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

which patients were asked to press any button box button using the 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 FM 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) 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 FM pain. Patients read the CAT statements on a laptop to familiarize themselves 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 statement blocks was pseudorandomized (Figure 1). After the scan, patients again completed the CAQ and CAT Valence Questionnaire (CVQ), the latter of 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 about before and after the 2 fMRI runs.

Psychophysiologic response was also assessed, as phasic HR 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 (EKG) was collected during scanning using an MR-compatible system (MP150; Biopac Systems). EKG peaks were annotated using in-house algorithms (MatLab 8.3) to estimate HR responses to CAT and NEU statements relative to a prestimulus baseline. Based on a peristimulus plot showing an average time series of response (Figure 2A), average HR was calculated for windows of 4–8 seconds from the onset of

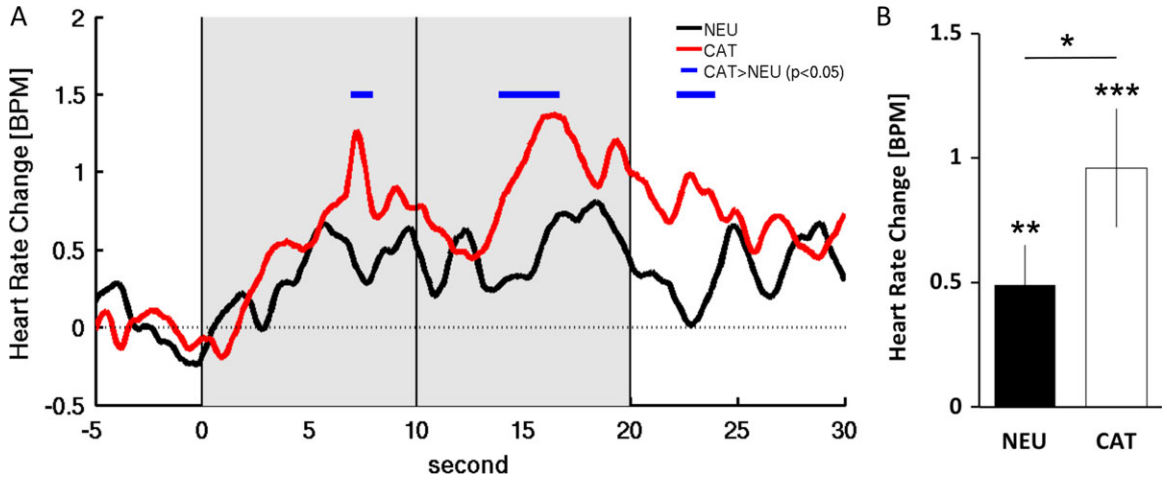

Figure 2. Heart rate (HR) responses to catastrophizing (CAT) and neutral (NEU) statements. **A,** Average HR time series data show different patterns during CAT and NEU statement blocks. **B,** The HR increase in response to CAT statements was significantly greater than the HR increase in response to NEU statements. Values are the mean ± SEM. ** = $P < 0.01$; *** = $P < 0.001$ versus baseline. * = $P < 0.05$. bpm = beats per minute. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.40507/abstract.

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 statement block. Differences in normalized HR response between CAT and NEU statement blocks were calculated, and significance ($P < 0.05$) was determined using a paired *t*-test (SPSS software version 10.0.7).

MRI data acquisition. MRI data were obtained on a 3.0T Siemens Skyra (Siemens Medical) equipped with a 32-channel head coil at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital. T1-weighted structural images were obtained using a 3-dimensional magnetization-prepared rapid gradient-echo pulse sequence (repetition time [TR] 2,530 msec, echo time [TE] 1.64 msec, flip angle 7°, field of view [FOV] 256 × 256 mm, spatial resolution 1 × 1 × 1 mm). Functional data (228 volumes/run) were obtained with a simultaneous multislice imaging pulse sequence for improved spatiotemporal resolution (acceleration factor 5, TR 1,250 msec, TE 33 msec, flip angle 65°, FOV 196 × 196 mm, voxel dimensions 2 × 2 × 2 mm, 75 axial slices with no gap) (29).

MRI data processing and analysis. Functional MRI data processing was carried out using FMRIB Software Library (FSL [fsl.fmrib.ox.ac.uk]), 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 FSL-FUGUE), skull stripped (FSL-BET), spatially smoothed (Gaussian kernel, full-width half-maximum 5 mm), and temporal high-pass filtered (cutoff 80 seconds) to remove signal drift noise. We used the following head motion exclusion criteria: framewise displacement and rotation >2 mm and 2°, respectively. For coregistration of structural and functional data to standard Montreal Neurological Institute (MNI) space (FSL-FNIRT), structural images were aligned to fMRI data (BBREGISTER).

A first-level, within-subject, generalized linear model (GLM) analysis was performed by modeling CAT and NEU statement 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 2 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 Nonlinear Image Registration Tool (FNIRT) and used for group analysis (i.e., CAT and NEU statement group map, and CAT versus NEU statement difference map) using FMRIB Local Analysis of Mixed Effects (FLAME 1+2, cluster-corrected for multiple comparisons, $Z > 2.3$, $P < 0.05$).

The CAT versus NEU statement 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 (https://www.nitrc.org/projects/caret/) 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 resting-state fMRI parcellation based on 1,000 subjects (30).

RESULTS

Of 35 enrolled FM patients, 31 were included in the analyses (mean ± SD age 43.74 ± 11.71 years; 26 Caucasians, 2 African Americans, 1 Asian, 1 Cape Verdean, and 1 of unknown ethnicity) (for medications the 31 patients used at the time of scanning, see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40507/abstract). Four FM patients were excluded from analyses (2 due to structural brain abnormalities, 1 due to inability to comply with

MRI safety requirements, and 1 because of falling asleep during fMRI [the patient failed to respond to the catch trial, which the patient confirmed retrospectively]).

Clinical measures. FM patients reported moderate-to-high scores on the PCS (mean ± SD 21.03 ± 12.92), BPI subscales (4.74 ± 1.87 for severity, 5.13 ± 2.41 for interference), and PROMIS-29 subscales (39.89 ± 6.96 for physical function, 56.73 ± 8.13 for anxiety, 53.68 ± 8.97 for depression, 58.73 ± 8.13 for sleep disturbance, 46.96 ± 13.91 for satisfaction with participation in social roles) at the initial behavioral visit. After 2 CAT task fMRI runs, patients reported higher CAQ (statement applicability) scores for CAT statement blocks compared to CAQ scores for NEU statement blocks (mean ± SD CAQ_{CAT} score 6.90 ± 4.64 versus CAQ_{NEU} score 2.03 ± 2.93; $P < 0.0001$). Mean ± SD CVQ scores demonstrated that CAT statements were indeed perceived as affectively negative (CVQ_{CAT} score −57.86 ± 37.68), while NEU statements were not perceived as having negative valence (CVQ_{NEU} score 7.88 ± 19.00) ($P < 0.00001$ for CAT statements versus NEU statements) (Table 1). Mean ± SD state anxiety levels showed no significant difference between before and after 2 CAT task fMRI runs (21.25 ± 18.54 for before versus 21.32 ± 20.02 for after; $P = 0.93$ [n = 28 patients]).

PCS scores correlated positively with CAQ_{CAT} scores ($r = 0.81$, $P < 0.0001$), the BPI interference subscale ($r = 0.45$, $P < 0.05$), and PROMIS-29 subscales (for anxiety, $r = 0.73$, $P < 0.0001$; for depression, $r = 0.66$, $P < 0.0001$). Furthermore, CAQ_{CAT} scores correlated positively with the BPI interference subscale ($r = 0.52$, $P < 0.01$) and PROMIS-29 subscales (for anxiety, $r = 0.69$, $P < 0.0001$; for depression, $r = 0.60$, $P < 0.0001$; for sleep disturbance, $r = 0.39$, $P < 0.05$; for satisfaction with participation in social roles, $r = -0.37$, $P < 0.05$).

Brain and psychophysiologic responses during catastrophizing. Data from all 31 FM patients were available for fMRI analysis, as all patients passed head motion exclusion criteria. To assess psychophysiologic arousal, we quantified HR responses and found greater HR increases during CAT statements (mean ± SEM 0.96 ± 0.24 beats per minute) than during NEU statements (0.49 ± 0.16 beats per minute) ($P = 0.03$) (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 [vlPFC] and posterior superior temporal sulcus) (see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40507/abstract). The CAT-NEU statement difference map revealed a significant positive contrast in the left ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC, respectively), precuneus, left vlPFC, left angular gyrus/inferior parietal lobule (IPL), left medial prefrontal cortex (mPFC), and right cerebellum. Most of the CAT-NEU statement clusters were within the boundaries of the DMN, as outlined in yellow (Figure 3) by DMN parcellation (30). The CAT-NEU statement difference map also showed a significantly negative contrast in the bilateral parietal lobule, left medial temporal lobe, and bilateral inferior temporal gyrus (temporo-occipital part) (Figure 3 and Table 2). Notably, as also evidenced by the group difference map bar plots (Figure 3) and group maps (see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40507/abstract), regions such as the PCC showed activation for CAT statements and deactivation for NEU statements, while for other DMN regions such as the mPFC, there was reduced deactivation for CAT statements compared to NEU statements, which also presented as a positive CAT-NEU statement contrast.

Association between CAT-specific brain responses and clinical/psychometric measures. We found that vPCC activation during CAT statements was positively correlated

Table 1. Demographics and clinical/psychometric measures of the 31 fibromyalgia patients*

Demographics	
Age, years	43.74 ± 11.71
Clinical pain measures	
Duration since symptom onset, years	7.65 ± 7.05
Brief Pain Inventory	
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 Scale score, 0–52	21.03 ± 12.92
CAT task–recalled pain experience	
Pain intensity, 0–100†	56.20 ± 19.00
Pain unpleasantness, 0–100‡	59.31 ± 20.24
CAQ score, 0–20	
Total CAQ_{CAT} score	6.90 ± 4.64
Total CAQ_{NEU} score	2.03 ± 2.93
P, CAQ_{CAT} score vs. CAQ_{NEU} score	<0.0001
CVQ score (−100 = negative, +100 = positive)	
Total CVQ_{CAT} score	−57.86 ± 37.68
Total CVQ_{NEU} score	7.88 ± 19.00
P, CVQ_{CAT} score vs. CVQ_{NEU} score	<0.00001

* Values are the mean ± SD. PROMIS-29 = Patient-Reported Outcomes Measurement Information System 29-Item Profile; CAT = catastrophizing; CAQ = CAT Applicability Questionnaire (assessed the extent to which patients had thoughts or feelings described in statements while reflecting on their pain during the CAT task); CAQ_{CAT} = rating of applicability for CAT statement blocks; CAQ_{NEU} = rating of applicability for neutral (NEU) statement blocks; CVQ = CAT Valence Questionnaire (assessed patients' ratings of how positive or negative each statement was on a visual analog scale); CVQ_{CAT} = CVQ rating of CAT statements; CVQ_{NEU} = CVQ rating of NEU statements.
† Twenty-five patients.
‡ Twenty-six patients.

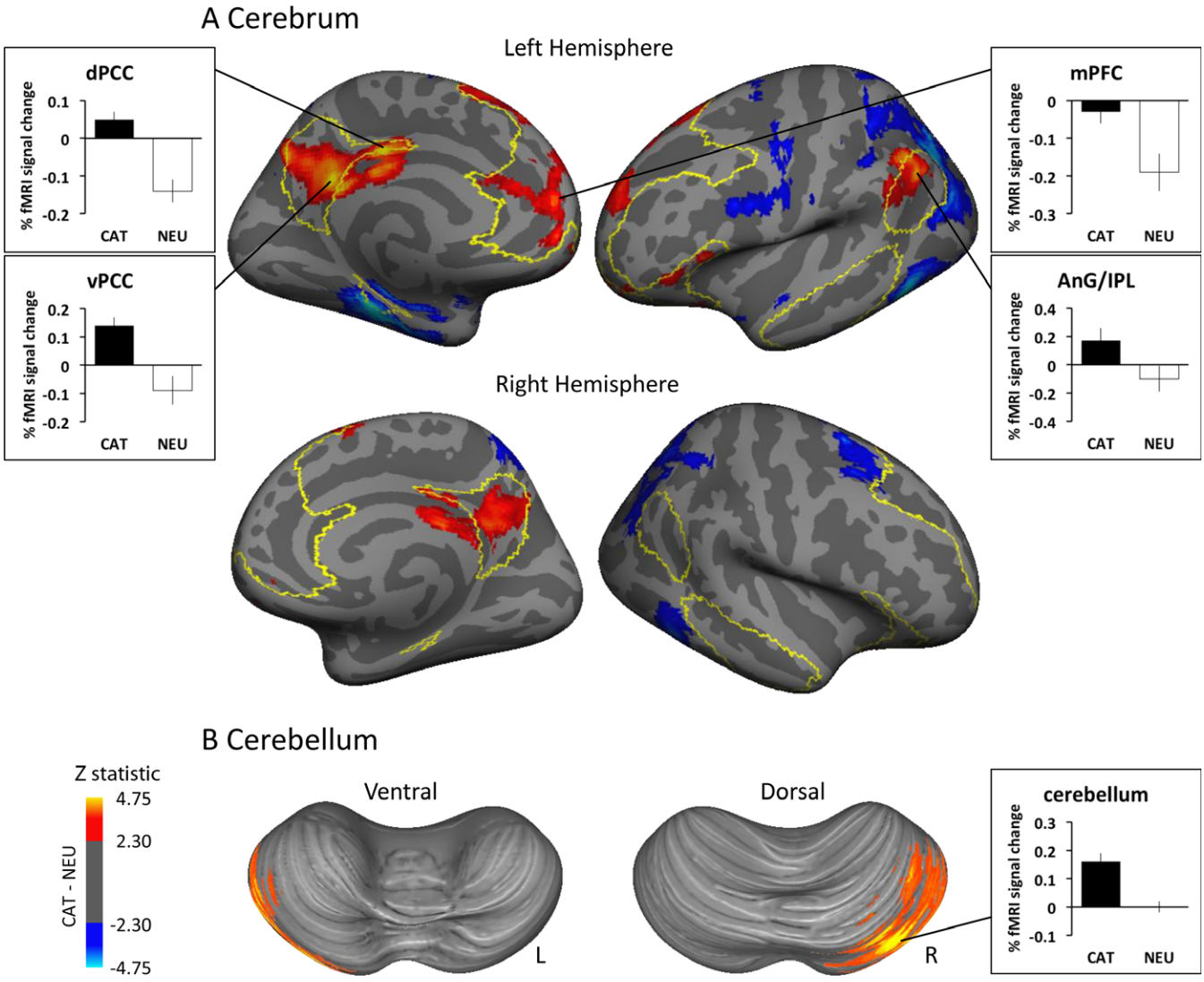

Figure 3. Brain responses during catastrophizing (CAT). **A,** Most of the clusters with positive contrast (more responses to CAT statements than to neutral [NEU] statements) in the cerebral cortex, including the ventral and dorsal posterior cingulate cortex (vPCC and dPCC, respectively), the medial prefrontal cortex (mPFC), and the angular gyrus/inferior parietal lobule (AnG/IPL), were within the boundary of the default mode network, as defined by the resting-state functional magnetic resonance imaging (fMRI) parcellation based on 1,000 subjects (**yellow outlines**) (see ref. 30). **B,** The right cerebellum demonstrated significant positive contrast (more responses to CAT statements than to NEU statements). Values are the mean ± SEM. L = left hemisphere; R = right hemisphere.

with the total CAQ_{CAT} score (r = 0.38, $P < 0.05$), while dPCC activation during CAT statements was positively correlated with the BPI subscales (r = 0.38, $P < 0.05$ for both severity and interference) (Figure 4). No other brain ROI showed significant correlation with these clinical/psychometric measures (e.g., for vPCC versus BPI severity subscale, r = 0.11, $P = 0.57$; for vPCC versus PCS score, r = 0.20, $P = 0.27$; for vPCC versus PROMIS-29 anxiety subscale, r = 0.20, $P = 0.30$; for vPCC versus PROMIS-29 depression subscale, r = 0.17, $P = 0.37$; for dPCC versus CAQ_{CAT} score, r = 0.28, $P = 0.13$).

DISCUSSION

Pain catastrophizing plays a substantial role in the pathophysiology of FM. In this study, 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 FM 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

Table 2. Brain response on functional magnetic resonance imaging during catastrophizing task*

		Location, mm†				Z score, mean ± SD	
	Size, mm^3	X	Y	Z	Z score	CAT statements	NEU statements
CAT statements > NEU statements							
Cerebellum, right hemisphere	21,448	32	−74	−38	5.26	1.79 ± 1.51	0.04 ± 1.22
dPCC, left hemisphere	2,576	−2	−20	36	5.10	0.64 ± 1.66	−1.16 ± 1.93
vPCC, left hemisphere	6,848	−4	−42	26	4.95	1.32 ± 1.83	−0.90 ± 2.32
PC, left hemisphere	6,848	−4	−72	38	4.65	1.34 ± 2.36	−0.45 ± 2.90
Angular gyrus, left hemisphere	10,512	−44	−62	36	4.43	0.77 ± 1.79	−0.60 ± 2.05
Pre-SMA/SMA, left hemisphere	6,440	−14	20	62	4.02	1.33 ± 1.55	0.27 ± 1.78
vlPFC, left hemisphere	1,984	−50	22	0	4.27	2.78 ± 2.06	1.38 ± 1.68
dlPFC, left hemisphere	6,240	−20	56	28	4.00	1.03 ± 1.68	−0.39 ± 1.56
mPFC, left hemisphere	6,240	−12	54	10	3.75	−0.02 ± 1.33	−1.17 ± 1.60
CAT statements < NEU statements							
MTL, left hemisphere	30,248	−34	−30	−20	−5.21	−0.96 ± 1.37	1.26 ± 2.06
IPL, left hemisphere	21,128	−28	−70	36	−4.99	2.59 ± 2.94	4.86 ± 3.32
IPL, right hemisphere	14,576	42	−76	26	−4.05	−1.60 ± 2.55	−0.55 ± 2.29
SPL, left hemisphere	21,128	−16	−56	58	−3.75	−0.69 ± 1.99	0.32 ± 2.08
SPL, right hemisphere	14,576	12	−60	58	−3.87	−1.02 ± 2.44	0.31 ± 2.38
ITG, left hemisphere	30,248	−46	−54	−14	−5.73	1.80 ± 2.57	3.87 ± 3.05
ITG, right hemisphere	6,312	60	−60	−14	−3.80	−0.74 ± 1.25	0.37 ± 1.45
Premotor area, left hemisphere	7,504	−31	−4	66	−3.48	−0.07 ± 1.31	0.66 ± 1.36
Premotor area, right hemisphere	6,288	28	14	58	−4.02	−1.23 ± 1.89	0.04 ± 1.94
M1, left hemisphere	7,504	−42	−10	46	−3.48	0.68 ± 1.39	1.47 ± 1.78

* CAT = catastrophizing; NEU = neutral; 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 lobe; IPL = inferior parietal lobule; SPL = superior parietal lobule; ITG = inferior temporal gyrus; M1 = primary motor cortex.
† By standard Montreal Neurological Institute space.

high interpatient variability. Compared to neutral statements, reflection on pain catastrophizing statements was encoded by activation of the ventral (posterior) and dorsal (anterior) posterior cingulate cortex (vPCC and dPCC) in addition to other, mainly DMN, brain regions. Importantly, the vPCC and dPCC were the only brain areas that showed a positive correlation between catastrophizing-related activation (CAT-NEU statements) 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., the BPI score) were associated with dPCC activation. Taken together, these findings suggest that the posterior cingulate cortex encodes pain catastrophizing in FM.

While previous 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 the mPFC and increases the PCC response to evoked pain stimuli in healthy adults (16). In fact, previous research has consistently shown reduced DMN deactivation in chronic pain patients in response to a range of externally focused tasks (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 the vPCC in response to catastrophizing about FM pain but also a significant association between vPCC activity and the CAQ score. The PCS score was positively correlated with the 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 the dPCC also plays a broader role in attentional focus,

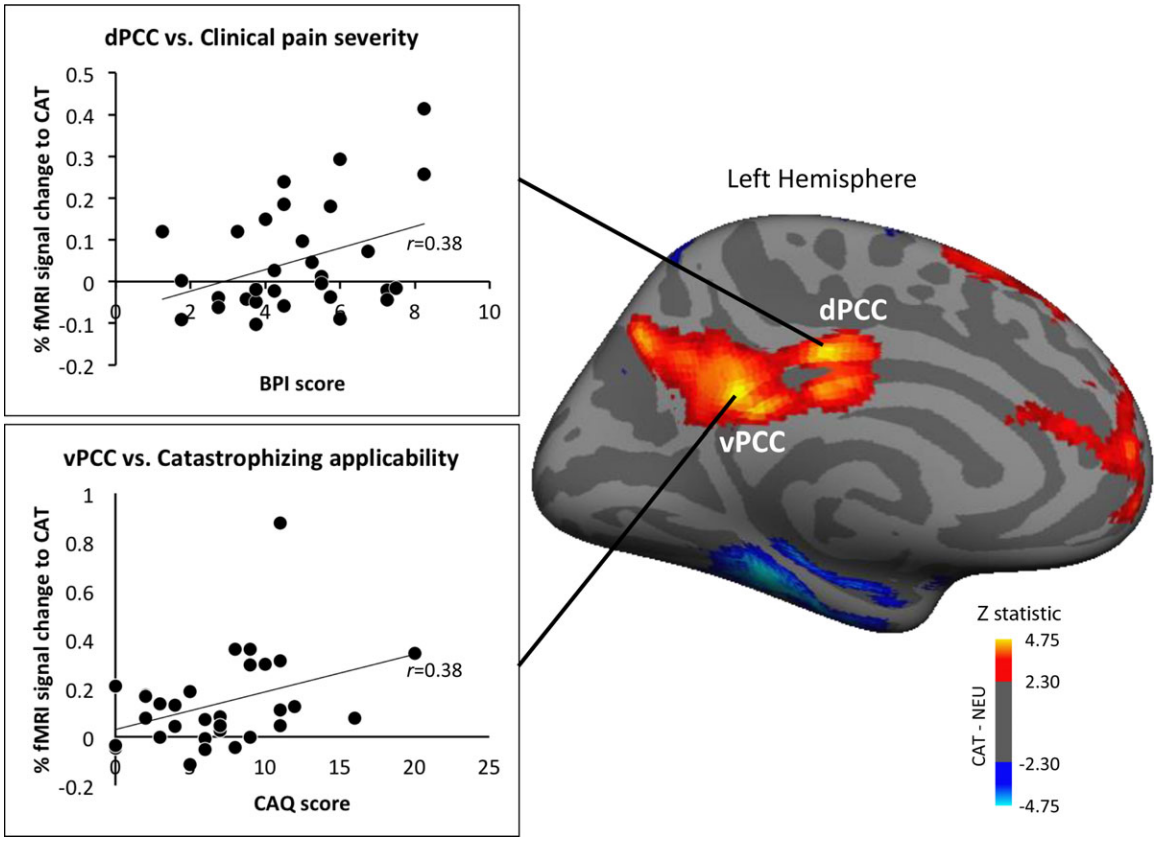

Figure 4. Regions from the catastrophizing–neutral (CAT-NEU) statement difference map demonstrating an association with clinical/psychometric measures. The response of the dorsal posterior cingulate cortex (dPCC) to CAT statements was positively correlated with clinical fibromyalgia pain severity on the Brief Pain Inventory (BPI), and the response of the ventral posterior cingulate cortex (vPCC) to CAT statements was positively correlated with ratings of catastrophizing applicability (i.e., the CAT Applicability Questionnaire [CAQ] score). fMRI = functional magnetic resonance imaging. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.40507/abstract.

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 and found increased combined levels of glutamate and glutamine (Glx) in FM for a PCC subregion consistent with the vPCC, suggesting increased excitatory neurotransmission in this area (36). Importantly, greater levels of Glx were positively correlated with greater trait PCS scores. Another study noted that increased connectivity between the 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 the 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. Thus, 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, the PCS score was not associated with vPCC activation in response to our CAT task, suggesting that greater activation (compared to neutral statements) is more of a state phenomenon, while altered connectivity and Glx levels for the vPCC may reflect more stable trait catastrophizing. Additional support for a phasic response is provided by the lack of a post-run increase in general

anxiety levels, which suggests 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 statement blocks (as supported by elevated psychophysiologic responses), but not in subsequent statement blocks or post-run ratings.

We also found that dPCC activity, which was increased during CAT statements compared to NEU statements, was positively correlated with FM pain severity and interference scores. This association suggests a differential function of the dPCC, compared to the vPCC, during catastrophizing. PCC subregions consistent with the dPCC cluster we identified were functionally connected not only to other DMN regions but also to regions of central executive and even sensorimotor networks (33). Similarly, Vogt et al have also shown heterogeneity of the PCC based on cytoarchitecture and resting glucose metabolism of PCC subregions, suggesting that the vPCC plays an important role in self-monitoring, while the dPCC interacts more with the cingulate motor area and is related to motor and nociceptive information processing (34).

Thus, the 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 therefore 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, the 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 a 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 the 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 the PCC has commonly been linked with self-referential cognition, while the mPFC is activated by negative mood induction (16), and its connectivity with the PCC is increased in conjunction with rumination about chronic pain (37). Increased IPL activity has also been reported in response to painful pressure stimulation in FM patients (9) and has also been shown to be involved in emotion processing (46). Cerebellum (Crus I and II, posterior cerebellum, higher fMRI signal increase during CAT statements than during NEU statements) activity and connectivity (47) have 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, the significantly greater psychophysiologic (HR increases) response during CAT statement blocks compared to NEU statement blocks suggests greater cognitive/affective engagement by patients with 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., the 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 statement blocks, as we did not want to encroach on their self-referential rumination with thought probe ratings. We instead used cardioautonomic psychophysiologic 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 the ventral (posterior) and dorsal (anterior) posterior cingulate cortex (the 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 current study enhances the clinical relevance of previous 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 brains during engagement in catastrophizing about past episodes of their clinical pain. These findings provide evidence that the posterior cingulate cortex may support pain catastrophizing in FM, and they 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lee, Protsenko, Lazaridou, Ellingsen, Mawla, Loggia, Wasan, Edwards, Napadow.

Acquisition of data. Lee, Protsenko, Lazaridou, Franceschelli, Ellingsen, Mawla, Isenburg, Berry, Galenkamp.

Analysis and interpretation of data. Lee, Protsenko, Ellingsen, Mawla, Isenburg, Berry, Loggia, Edwards, Napadow.

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DOI 10.1002/art.40658

Erratum

In the article by Saag et al in the January 2017 issue of *Arthritis & Rheumatology* (pages 203–212), text in the fourth paragraph on page 211, regarding lesinurad prescribing information, was incorrect. The paragraph should have read "Of note, the US prescribing information for lesinurad recommends assessment of renal function prior to initiation of therapy, with initiation contraindicated in patients with creatinine clearance <45 ml/minute. Renal function should be assessed periodically after initiation of therapy, with discontinuation recommended if creatinine clearance persistently falls below 45 ml/minute. Lesinurad is contraindicated in subjects with severe renal impairment, end-stage renal disease, kidney transplant recipients, and patients on dialysis."

We regret the error.