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Original Reports

The Lateral Prefrontal Cortex Mediates the Hyperalgesic Effects of Negative Cognitions in Chronic Pain Patients

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Abstract: Although high levels of negative affect and cognitions have been associated with greater pain sensitivity in chronic pain conditions, the neural mechanisms mediating the hyperalgesic effect of psychological factors in patients with pain disorders are largely unknown. In this cross-sectional study, we hypothesized that 1) catastrophizing modulates brain responses to pain anticipation and 2) anticipatory brain activity mediates the hyperalgesic effect of different levels of catastrophizing in fibromyalgia (FM) patients. Using functional magnetic resonance imaging, we scanned the brains of 31 FM patients exposed to visual cues anticipating the onset of moderately intense deep-tissue pain stimuli. Our results indicated the existence of a negative association between catastrophizing and pain-anticipatory brain activity, including in the right lateral prefrontal cortex. A bootstrapped mediation analysis revealed that pain-anticipatory activity in the lateral prefrontal cortex mediates the association between catastrophizing and pain sensitivity. These findings highlight the role of the lateral prefrontal cortex in the pathophysiology of FM-related hyperalgesia and suggest that deficits in the recruitment of pain-inhibitory brain circuitry during pain-anticipatory periods may play an important contributory role in the association between various degrees of widespread hyperalgesia in FM and levels of catastrophizing, a well-validated measure of negative cognitions and psychological distress.

***Perspective:** This article highlights the presence of alterations in pain-anticipatory brain activity in FM. These findings provide the rationale for the development of psychological or neurofeedback-based techniques aimed at modifying patients' negative affect and cognitions toward pain.*

***Key words:** Fibromyalgia, catastrophizing, negative affect, functional magnetic resonance imaging, psychophysics.*

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Fibromyalgia (FM) is a chronic common disorder characterized by persistent, widespread pain and myofascial tenderness. It is a primary cause of disability and one of the most challenging-to-treat rheumatologic conditions.[41] The diversity of symptoms reported by FM patients is consistent with the view that FM is a pervasive nervous system disorder involving a complex interaction of biopsychosocial mechanisms. Although recent evidence of small-fiber neuropathy suggests that peripheral alterations contribute to the pathophysiology of FM in a subset of patients,[26,45] it is well established that negative cognitive and affective factors play a prominent role in maintaining pain and disability in this and other pain disorders.[6] In fact, FM is characterized by a strong association with psychiatric comorbidities, including anxiety and depression, and has been considered an affective spectrum disorder.[16] Catastrophizing is a pain-specific psychosocial construct composed of cognitive and emotional processes such as helplessness, pessimism, rumination about pain-related symptoms, and magnification of pain complaints. Although catastrophizing positively correlates with general measures of negative affect such as depressive symptoms, anxiety, or neuroticism, it also shows a unique and specific influence on pain-related outcomes.[6] Several brain imaging studies have found that greater catastrophizing in FM patients, compared to healthy controls, was associated with enhanced pain-evoked activation in dorsolateral and medial prefrontal and dorsal anterior cingulate cortices.[12] However, the brain mechanisms mediating the hyperalgesic effect of catastrophizing are unknown.

In addition to catastrophizing and hyperalgesia, FM patients also demonstrate lower brain reactivity to pain-anticipatory cues (as well as to relief-anticipatory cues) than healthy individuals.[21] This observation, which we argued may be in part the result of the alterations in dopaminergic[53,54] and/or GABAergic[10] neurotransmission that have been documented in these patients, adds to a growing literature supporting reduced responsiveness of FM patients to a variety of experimental manipulations.[19,44,54]

The pain experience can be dramatically shaped by anticipatory processes, and the brain state preceding a painful stimulation has been shown to predict responses to experimental,[2,31] as well as clinical, pain.[23] Thus, in the present study, we used functional magnetic resonance imaging (fMRI) and mediation analyses in a cohort of patients with FM and a wide range of catastrophizing scores to test the hypotheses that 1) individual levels of catastrophizing modulate brain responses to pain anticipation in FM and 2) anticipatory brain activity mediates the hyperalgesic effect of higher catastrophizing.

Methods

Subjects

One hundred four FM patients (n = 13 male) were initially screened by phone for probable eligibility to participate in this experiment at the Brigham and Women's Hospital Pain Management Center and Martinos Center for Biomedical Imaging at Massachusetts General Hospital in Boston, Massachusetts. Patients were screened and enrolled over a 16-month period between September 2010 and December 2011. Of the 104 patients initially contacted, 53 (n = 7 male) signed a consent form and were invited for a screening visit; the others were either not interested (n = 18) or ineligible (most commonly due to claustrophobia, being on opioids, or having peripheral neuropathy) (n = 22) or had scheduling conflicts (n = 11). Of the subjects who were invited to the screening visit, 5 were determined to be ineligible and excluded at the behavioral session (for implanted metal, leg edema, or neuropathy) and 4 subsequently dropped out. Of the remaining 44 (n = 6 male) who proceeded to the scan visit, only 31 (n = 4 male) had complete and analyzable data for the purposes of the present study. Thus, 13 subjects did not successfully complete the fMRI scanning noted below because of inability to tolerate pain procedures (n = 5), scanner time constraints (n = 4), and scanner/equipment failure (n = 4).

Average age (mean ± standard deviation) was 44.0 ± 11.9, symptom duration was 12.5 ± 12.2 years, and current clinical pain intensity was 34.3 ± 25.2 (out of 100). For additional details on the patients' clinical and demographic characteristics, please refer to our previous publication.[21] Enrolled patients were diagnosed with FM (as confirmed by physician and medical records) and also met the recently proposed Wolfe et al criteria,[52] which require the presence of widespread pain and endorsement of multiple somatic and cognitive symptoms. Exclusion criteria included younger than age 18 years; history of claustrophobia; neurologic disorders, including peripheral neuropathy; history of significant head injury; serious cardiovascular disease; current use of opioids; implanted medical or metallic objects; and pregnancy. Although these criteria led to a sizable number of excluded subjects following initial screening, the criteria were either necessary (eg, claustrophobia for MRI evaluation) or did not significantly compromise the generalizability of our study sample, as, for example, recent prospective studies and reviews point to a lack of evidence for the effectiveness of long-term opioid therapy in patients with FM, and consequently very few FM patients are on chronic opioids.[29] All participants in the study provided written informed consent in accordance with the hospitals' institutional review boards. This was an exploratory study designed to power a larger clinical trial.

Study Overview

After a training visit, which was used to familiarize subjects with the stimuli and rating procedures, subjects participated in a brain imaging visit on a separate date. At the beginning of the visit, the intensity of stimulation needed to achieve a pain intensity rating of ~50 out of 100 was assessed (for more details, see[21]). During a functional imaging scan run, the subjects' brain activity was investigated using blood oxygen level–dependent fMRI while they underwent 3 separate tonic (ie, 46–74 sec)

cuff pressure pain stimuli at the predetermined intensity level.

Cuff pain algometry (CPA) stimuli were delivered using a 13.5-cm-wide Velcro-adjusted pressure cuff connected to a rapid cuff inflator (Hokanson Inc, Bellevue, WA). CPA is a technique that has been successfully adopted in psychophysical investigations,[7,32–35] including in FM patients,[17] and in neuroimaging studies we recently conducted.[18,22] Among the advantages of CPA over other more commonly used methods of pain stimulation (eg, contact heat) is that CPA stimuli have a preferential effect on deep tissue nociceptors, such as in muscles,[34] and thus may better mimic clinical pain,[38] particularly in conditions characterized by myofascial tenderness, such as FM.

During the run, a fixation cross was presented visually using a mirror and projector system. The cross changed color (from black to green) 6 to 10 seconds prior to cuff inflation to signal the period of pain anticipation and then turned black again at stimulus onset. Another change in crosshair color (from black to blue) 6 to 12 seconds prior to stimulus offset induced anticipation of pain relief (not discussed here). Pain intensity and unpleasantness ratings were obtained at the end of each stimulus, 8 seconds after stimulus offset, using an MRI-compatible button box and the ePrime software (Psychology Software Tools, Sharpsburg, PA). The present study presents an analysis of a data set previously described.[21] As opposed to the previous study, which compared brain activity across groups, in the present study we employed statistical approaches aimed at evaluating the relationship among pain-anticipatory activity, pain sensitivity, and catastrophizing. Cuff pain sensitivity was the single main outcome measure of this study.

fMRI data were acquired using a 3-T Siemens TIM Trio MRI System (Siemens Medical, Erlangen, Germany) equipped for echo planar imaging with a 32-channel head coil. A whole-brain T2*-weighted gradient echo blood oxygen level–dependent echo planar imaging pulse sequence was used (repetition time [TR]/echo time [TE] = 2 seconds/30 milliseconds, flip angle = 90°, 32 anterior-to-posterior commissure aligned axial slices, voxel size = 3.1 × 3.1 × 4 mm). We also collected anatomical data using a multiecho magnetization-prepared rapid gradient-echo pulse sequence (TR/TE1/TE2/TE3/T4 = 2530/1.64/3.5/5.36/7.22 milliseconds, flip angle = 7°, voxel size = 1 mm isotropic). During the imaging procedures, electrocardiography and pneumobelt respiratory volume data were collected concurrently for the purpose of correction for cardiorespiratory artifacts in the fMRI data.

Catastrophizing was assessed at the first visit in all subjects using the Pain Catastrophizing Scale (PCS).[43] The PCS is a 13-item measure that asks respondents to self-report their tendency to catastrophize when in pain (eg, during "illness, injury, dental procedures or surgery"). Subjects rate from 0 ("not at all") to 4 ("all the time") 13 statements on "the degree to which (they) have these thoughts and feelings when (they) are experiencing pain." Factor analysis has revealed 3 PCS subscales, magnification, rumination, and helplessness, which are moderately to highly intercorrelated, and most studies use the total PCS score. A number of studies have replicated this factor structure using confirmatory factor-analytic methods in healthy adults, in chronic pain patients, across different age and cultural groups, and in non-English languages.[37] Moreover, the factor structure of the PCS appears to be invariant across sexes and across chronic pain patients versus pain-free controls.[5,28] PCS scores are highly stable over time, suggesting that the measure assesses trait-like properties. For example, a recent study of FM patients showed intraclass correlations in the range of .85 to .9 for 1-month test-retest reliability for multiple translations of the PCS in different linguistic groups.[25] Measures of catastrophizing are moderately correlated with general measures of negative affect (eg, symptom inventories for depression and anxiety), but in prospective studies, catastrophizing emerges as a unique predictor of adverse pain-related outcomes, such as the development of persistent pain, enduring pain-related disability, and elevated health care costs, making it a crucial target of study and treatment in pain populations.[6]

Statistical Analysis

fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool), version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Data were corrected for cardiorespiratory artifacts using RETROICOR.[11] Following this procedure, data were corrected for slice timing (slicetimer), motion (MCFLIRT), and B0 inhomogeneities (PRELUDE and FUGUE) and were skull stripped (BET), grand-mean intensity normalized by a single multiplicative factor, high-pass temporal filtered (Gaussian-weighted least-squares straight line fitting, with sigma = 72 seconds), and spatially smoothed (FWHM = 5 mm). Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Cortical surface reconstruction was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) for improved structural-functional coregistration, which was carried out using FreeSurfer's bbregister tool[15] and visualization purposes.

A first-level within-subject generalized linear model analysis was performed by modeling the pain anticipation cue as regressor of interest. We also modeled the cuff pain stimulus application, an anticipation of pain relief cue, the period between stimulus offset and rating periods, and the rating periods as regressors of no interest in the model (see[21]). A canonical double-gamma hemodynamic response function was adopted.

The first-level parameter estimate and corresponding variance maps were then registered to the MNI152 standard space using the FMRIB's Nonlinear Image Registration Tool (FNIRT) for group analyses. The relationship between catastrophizing and brain responses to pain anticipation was then assessed in a whole-brain voxelwise multiple linear regression, with the demeaned PCS score as an explanatory variable in a generalized linear model, using FLAME (FMRIB's Local Analysis of Mixed Effects) 1 + 2, with automatic outlier detection enabled.

The resulting statistical map was cluster corrected for multiple comparisons using a cluster-forming voxelwise threshold of Z >2.3 and a (corrected) cluster significance threshold of $P < .05$. For visualization purposes, the statistically significant clusters were projected to a standard surface (fsaverage).

We then tested the hypothesis that the association between catastrophizing scores (independent variable) and pain sensitivity (ie, the cuff pressure values needed to reach the target rating of 50/100 [the dependent variable]) was mediated by the pain-anticipatory brain activity (mediator variable, M). Although several regions demonstrated an association with catastrophizing (see the Results section), we elected to focus our mediation analysis on a single region (right lateral prefrontal cortex [lPFC], in a subregion extending over the anterior and ventral lPFC), as this region demonstrated the peak effect size (ie, largest contrast of parameter estimates value) in the regression analysis against the catastrophizing scores. The blood oxygen level–dependent percent signal change values (averaged over all voxels with a Z score ≥ 3) for this region were used as the M variable. The unstandardized path coefficients in this mediator model and the bootstrap 95% confidence intervals (CIs) for total and specific indirect effects of the independent variable on the dependent variable through M (5,000 bootstrap samples) were estimated using the Preacher and Hayes Indirect Mediation Analysis tool[36] for SPSS, version 20 (IBM Corp, Armonk, NY). As recommended, the indirect (ie, mediation) effect was considered statistically significant if the 95% CI did not include zero.

The association between catastrophizing and pain sensitivity was investigated by correlating the PCS scores and the cuff pressure values needed to reach the target rating of 50/100 (in mmHg). These behavioral analyses were performed with Statistica 10.0 (StatSoft Inc, Tulsa, OK), using an alpha level of .05.

Results

Psychophysical Analyses

Patient PCS scores showed broad individual variability (range = 0–46, mean ± standard deviation = 23.4 ± 13.6). As Fig 1 shows, PCS scores were negatively correlated with cuff pressure ($r = -.37$, $P < .05$), meaning that greater catastrophizing was associated with less cuff pressure needed to elicit similar pain ratings. No correlations were found between PCS scores and ratings of the patients' own clinical pain (intensity: $r = .05$, $P = .78$; unpleasantness: $r = .19$, $P = .30$).

Imaging Analyses

In whole-brain voxelwise analyses (Fig 2, Table 1), brain responses to pain anticipation were found to be negatively correlated to PCS scores in the right lPFC, superior parietal lobule, and precuneus. The pain-anticipatory activity of the lPFC region (Fig 3A) exhibited an association not only with the PCS scores, as revealed by the multiple linear regression analysis (Figs 2 and 3B, scatterplot shown for illustrative purposes), but also with the cuff pressure needed to achieve the target percept (Fig 3C). No brain regions demonstrated positive correlation to PCS.

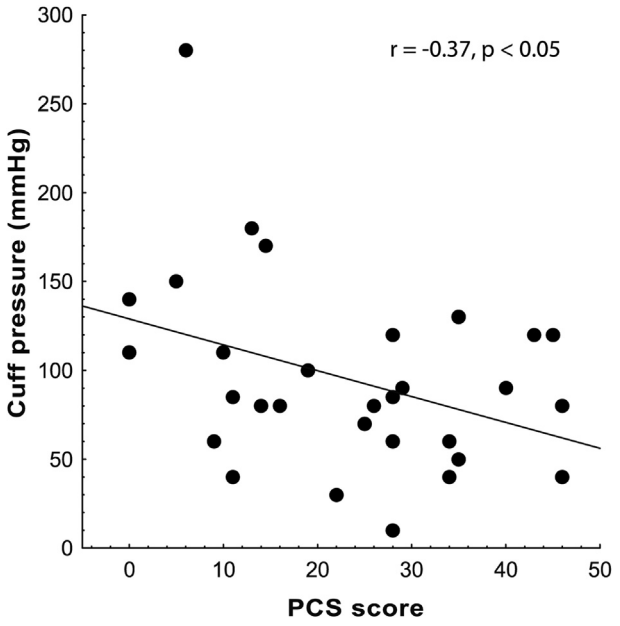

Figure 1. Psychophysical results. Catastrophizing scores correlated negatively with the pressure required to reach the target pain intensity rating.

Mediation Analyses

Because the pain-anticipatory activity of the right anterior/ventral lPFC was the most prominently associated with the catastrophizing scores and was also correlated with cuff pressure, we performed a bootstrapped mediation analysis to investigate the relation between these variables (Fig 3D). This analysis revealed that although the association between PCS and cuff pressure was statistically significant (path *c*; $\beta \pm$ bootstrap standard error $= -1.46 \pm .67$, $P < .05$), it was no longer significant after including the lPFC activity in the model (path *c'*; $\beta = -.82 \pm .73$, $P = .27$, nonsignificant). The bias-corrected 95% CIs for the specific indirect effect of PCS on cuff pressure through the lPFC activity (path $a \times b$; $\beta = -.63 \pm .54$) yielded a lower limit of -2.11 and an upper limit of $-.001$. As the CI did not include zero,[36] this analysis indicated that the association between catastrophizing and cuff pressure was significantly mediated by the pain-anticipatory activity of the anterior/ventral lPFC.

Discussion

Our results demonstrated that individual levels of catastrophizing were associated with reduced pain-anticipatory brain activity and that this reduced activity contributed to the hyperalgesic effect of catastrophizing in FM. More specifically, by using bootstrapped mediation analysis, we observed that the anticipatory activity of the lPFC mediated the association between levels of

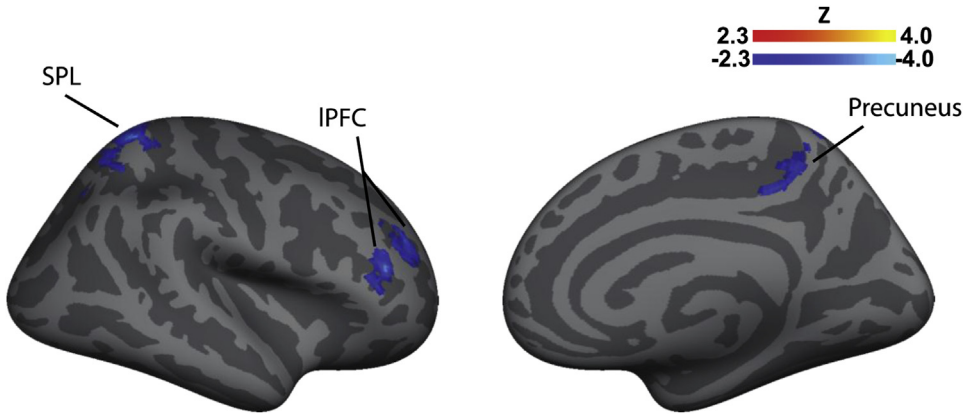

Figure 2. Catastrophizing is associated with pain-anticipatory brain activity. Whole brain linear regression analyses revealed that PCS scores were negatively correlated with pain-anticipatory activation in a widespread group of regions. Abbreviation: SPL, superior parietal lobule.

catastrophizing scores and mechanical (cuff) pain sensitivity.

Psychophysical studies have revealed that FM is associated with amplified central nervous system processing of nociceptive afference, with apparent enhancement of pain-facilitatory processes accompanying a reduction in endogenous pain inhibition.[4] Catastrophizing has shown similar associations, as elevated catastrophizing scores are linked with enhanced temporal summation and reduced effectiveness of conditioned pain modulation.[8,14,46,49] In agreement with these reports, we also observed that higher levels of catastrophizing in a population suffering from chronic pain were associated with elevated pain sensitivity—specifically, lower pressure values needed to achieve target pain intensity ratings (Fig 1). Furthermore, fMRI studies in healthy adults[42] and FM patients[12] have reported significant correlations between pain catastrophizing and evoked-pain brain responses in dorsolateral prefrontal, insula, and anterior cingulate cortices, that is, brain regions associated with emotional and motivational modulation of the pain experience. A recent study showed that inducing a depressed mood state increased levels of pain catastrophizing and broadly amplified cortical responses to a noxious stimulus.[1] Collectively, these findings strongly indicate that catastrophizing affects both brain processing and subjective reports of pain.

However, although high levels of catastrophizing have been associated in FM and other conditions with higher pain sensitivity and stronger brain activations within pain-processing areas, our knowledge of the brain mechanisms mediating the pain-amplifying effect of catastrophizing is still limited. By showing that lower pain-anticipatory lateral prefrontal activity mediates the hyperalgesic effect of catastrophizing, our study demonstrated that catastrophizing was associated with reduced engagement of the descending pain modulatory system, and more generally identified neural mechanisms underpinning the sensitizing effect of negative cognitive and emotional processes in chronic pain patients. Future studies will need to investigate whether our observations are specific to the effect of catastrophizing in FM or are generalizable to other chronic pain conditions.

The vlPFC and alPFC (also known as the frontal pole or the rostral frontal cortex[39]) are key brain regions involved in emotion regulation and implementation of cognitive strategies that reduce negative emotional experience, such as reappraisal.[3,27,51] These regions, predominantly right lateralized, have been implicated in high-level pain-modulatory mechanisms that are recruited when the pain experience is altered by changing expectations, beliefs, and judgments about pain.[20,30,40,47,50,51] In general, vlPFC activation is observed during pain anticipation,[21] including visceral pain,[24] and subjects with greater anticipatory vlPFC activation report less pain in response to uncontrollable noxious stimuli.[40] Moreover, enhanced activity in right

Table 1. Brain Regions Demonstrating a Significant Association Between Pain-Anticipatory Activity and Catastrophizing

		Local Maxima				
Cluster Size (No. of Voxels)	Cluster P Value	Z	x	y	z	Label
Positive correlations: not significant						
Negative correlations						
1,043	.00849	3.93	26	−48	64	Right superior parietal lobule
		3.31	2	−44	56	Right precuneus
843	.026	3.64	36	38	16	Right lPFC

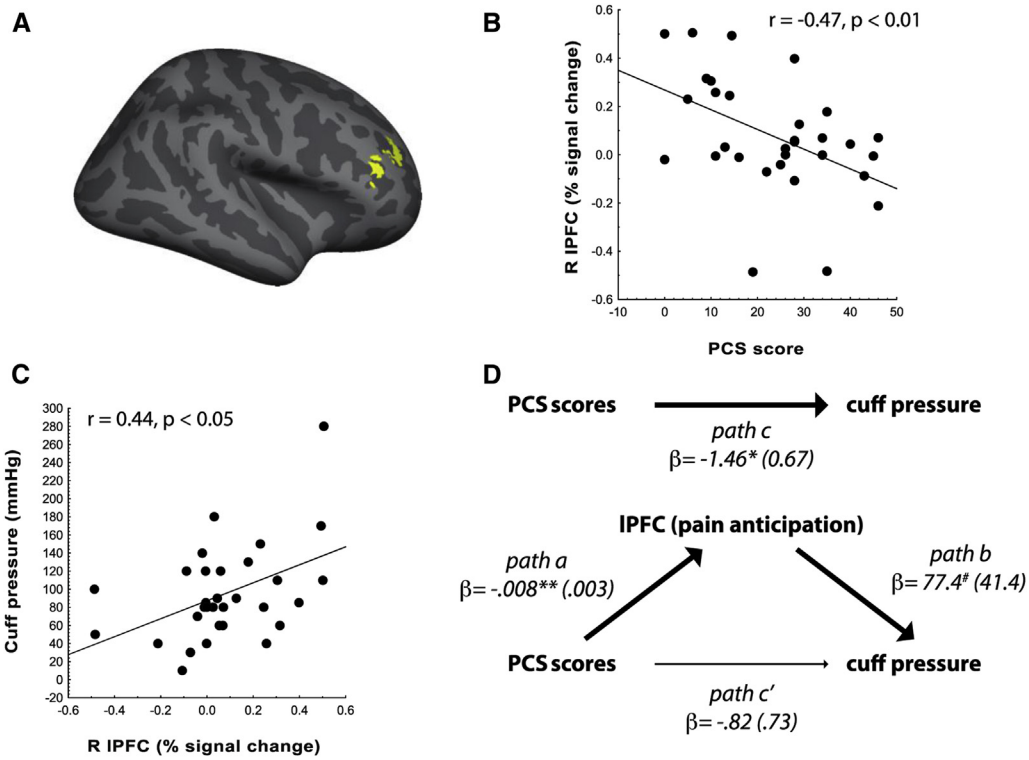

Figure 3. Pain-anticipatory activity of the lPFC mediates the effect of catastrophizing on pain sensitivity. **(A)** vlPFC/alPFC mask used to extract percent signal change for regression and mediation analyses. **(B** and **C)** The pain-anticipatory activity of this region correlated both with PCS **(B)** and cuff pressure needed to achieve the target pain intensity rating **(C)**. **(D)** A bootstrapped mediation analysis revealed that the relationship between PCS and cuff pressure was significantly mediated by vlPFC/alPFC activity. Path coefficients are unstandardized. Values within parentheses represent bootstrap standard errors. #*P* = .07, **P* < .05, ***P* < .01.

vlPFC predicts placebo-related symptom improvement in irritable bowel syndrome, which is mediated by attenuated activity of the dorsal anterior cingulate cortex during visceral stimulation.[20] Similarly, the activity of the alPFC was found to be more activated during self-controlled than during externally controlled pain stimulation and to mediate the analgesic effect of perceived control over pain.[51] Given the role of the lPFC in high-level pain-modulatory mechanisms, our findings suggest the possibility that catastrophizing induces hyperalgesia by disrupting the adaptive recruitment of vlPFC/alPFC-dependent pain-inhibitory processes, which normally attenuate the effects of incoming painful stimulation. Of note, altered vlPFC physiology in FM has also been reported using magnetic resonance spectroscopy, which demonstrated neurochemical alterations (ie, increased glutamate/glutamine concentration) in this region.[9] Thus, our results provide further evidence implicating the lPFC in FM pathophysiology. However, in the absence of a comparison with well-powered groups of healthy volunteers and other pain patients, from our study it is impossible to assess whether the mediational role of lPFC on the hyperalgesic effect of catastrophizing is unique to FM. In particular, future work in this area may benefit from investigating other pain conditions that involve central sensitization–like processes. Additionally, future studies should further investigate the mechanisms underlying the inverse relationship between catastrophizing and PFC activity. For instance, it is possible that this phenomenon is due to a heightened tonic activation of this structure in high catastrophizers, a hypothesis that would be best tested with other imaging modalities more sensitive to the detection of sustained activation, such as arterial spin labeling.[48]

When interpreting our results, it is important to keep in mind that mediation analyses are not sufficient to demonstrate the presence of a directional effect. In order to provide further corroboration of our interpretation on the role of lPFC as mediating the hyperalgesic effects of catastrophizing, other designs will need to be adopted (for instance, by monitoring the effects of lPFC neuromodulation on the relation between PCS and pain sensitivity, or by evaluating the effects of cognitive behavioral therapy aimed at reducing catastrophizing). Another factor complicating the interpretation of our observation is that it is extremely difficult to assess whether patients with high catastrophizing expressed higher pain ratings because they were genuinely more sensitive to pain or because they exhibited greater report bias. However, our previous study[21] as well as others' (eg,[13]) have shown that FM patients demonstrate pain-related brain activations very similar to healthy controls' when expressing similar amounts of pain, even despite large differences in nociceptive stimulus intensity. Though not definitive, these observations support our contention that ratings expressed by FM subjects reflect their subjective pain

experience, rather than report bias. Finally, it should be noted that the sample size of our data set was relatively small for mediation analyses. Therefore, although our observations are compatible with the literature implicating the lPFC in emotion regulation, reappraisal, and pain modulation,[3,20,27,30,40,47,50,51] they will need to be further corroborated in the context of studies with larger samples.

In sum, our results highlight the role of the lPFC in shaping the impact of negative cognitive and emotional processes on the experience of pain in a clinical population. Such findings have implications for understanding the pathophysiology and optimal treatment of FM and may help to identify the pathways by which pharmacologic and nonpharmacologic interventions, such as cognitive-behavioral therapy, can reduce pain and hyperalgesia in patients with persistent widespread pain.

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