Arthritis & Rheumatology
Vol. 0, No. 0, Month 2020, pp 1–11
DOI 10.1002/art.41220

American College of Rheumatology
Empowering Rheumatology Professionals

Aberrant Salience? Brain Hyperactivation in Response to Pain Onset and Offset in Fibromyalgia

Catherine S. Hubbard,[1] Asimina Lazaridou,[2] Christine M. Cahalan,[2] Jieun Kim,[3] Robert R. Edwards,[4] Vitaly Napadow,[5] and Marco L. Loggia[5]

Objective. While much brain research on fibromyalgia (FM) focuses on the study of hyperresponsiveness to painful stimuli, some studies suggest that the increased pain-related brain activity often reported in FM studies may be partially explained by stronger responses to salient aspects of the stimulation rather than, or in addition to, the stimulation's painfulness. Therefore, this study was undertaken to test our hypothesis that FM patients would demonstrate elevated brain responses to both pain onset and offset—2 salient sensory events of opposing valences.

Methods. Thirty-eight FM patients (mean ± SD age 46.1 ± 13.4 years; 33 women) and 15 healthy controls (mean ± SD age 45.5 ± 12.4; 10 women) received a moderately painful pressure stimulus to the leg during blood oxygen level–dependent (BOLD) functional magnetic resonance imaging. Stimulus onset and offset transients were analyzed using a general linear model as stick functions.

Results. During pain onset, higher BOLD signal response was observed in FM patients compared to healthy controls in dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC, respectively), orbitofrontal cortex (OFC), frontal pole, and precentral gyrus (PrCG). During pain offset, higher and more widespread BOLD signal response was demonstrated in FM patients compared to controls in frontal regions significantly hyperactivated in response to onset. In FM patients, some of these responses were positively correlated with pain unpleasantness ratings (VLPFC, onset; r = 0.35, $P = 0.03$), pain catastrophizing scores (DLPFC, offset; r = 0.33, $P = 0.04$), or negatively correlated with stimulus intensity (OFC, offset; r = –0.35, $P = 0.03$) (PrCG, offset; r = –0.39, $P = 0.02$).

Conclusion. Our results suggest that the increased sensitivity exhibited by FM patients in response to the onset and offset of painful stimuli may reflect a more generalized hypersensitivity to salient sensory events, and that brain hyperactivation may be a mechanism potentially involved in the generalized hypervigilance to salient stimuli in FM.

INTRODUCTION

Fibromyalgia (FM) is a poorly understood condition characterized by a constellation of symptoms including chronic widespread musculoskeletal pain and tenderness, extreme fatigue, and disturbances in mood, cognition, sleep, and memory (1–3). While the pathogenesis of FM is not well understood, the current consensus is that this condition is principally a disorder of central origin, arising from sensitized afferent nociceptive circuits and/or disrupted descending pain modulatory signaling, which in turn leads to widespread amplification of pain (1,4–6) (although some studies have provided evidence of peripheral changes in a subgroup of FM patients [7,8]). This persistent state of heightened central nervous system (CNS) reactivity or central pain amplification often manifests clinically with increased sensitivity to painful stimuli (hyperalgesia) and the tendency to perceive nonpainful stimuli as painful (allodynia).

Psychophysical studies utilizing quantitative sensory testing (QST) have shown that FM patients, when subjected to levels of stimulus intensity equivalent to those in healthy controls, report

Supported by the NIH (National Center for Research Resources grants P41-RR-14075, S10-RR-021110, and S10-RR-023043). Dr. Napadow's work was supported by the NIH (National Center for Complementary and Integrative Health grant P01-AT-006663 and National Institute of Arthritis and Musculoskeletal and Skin Diseases grant R01-AR-064367). Dr. Loggia's work was supported by the NIH (National Institute of Neurological Disorders and Stroke grant R01-NS-094306-01A1), the International Association for the Study of Pain (Early Career Research grant), and the US Department of Defense (grant W81XWH-14-1-0543).

[1]Catherine S. Hubbard, PhD: Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts; [2]Asimina Lazaridou, PhD, Christine M. Cahalan, BS: Brigham and Women's Hospital, Boston, Massachusetts; [3]Jieun Kim, PhD: Massachusetts General Hospital, Charlestown; [4]Robert R. Edwards, PhD: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [5]Vitaly Napadow, PhD, Marco L. Loggia, PhD: Harvard Medical School, Massachusetts General Hospital, and Brigham and Women's Hospital, Boston, Massachusetts.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Marco L. Loggia, PhD, Massachusetts General Hospital, A. A. Martinos Center for Biomedical Imaging, 149 Thirteenth Street, Room 2301, Charlestown, MA 02129. E-mail: marco.loggia@mgh.harvard.edu.

Submitted for publication October 11, 2019; accepted in revised form January 28, 2020.

greater perceived pain to a variety of sensory stimuli, including mechanical (deep blunt pressure), thermal (heat and cold), and electrical stimuli (9,10). Moreover, compared to controls, FM patients exhibit markedly reduced pain thresholds, potentiated temporal summation, and attenuated descending pain modulatory responses (11,12). Neuroimaging studies complement and extend these findings by providing a glimpse into the putative neural substrates underlying the pathophysiology of FM. For example, FM patients relative to controls display altered structural, neurochemical, neuroinflammatory, and brain network connectivity patterns as well as augmented brain responses to painful and nonpainful somatosensory stimuli in sensory-discriminative (e.g., primary and secondary somatosensory cortex), affective-motivational (e.g., cingulate and insular-opercular regions), and cognitive-attentional (e.g., dorsolateral prefrontal cortex) pain processing areas, as well as regions involved in the processing of punishing and rewarding events (ventral tegmental area) (13–20).

In addition to heightened pain perception and augmented pain-related brain responses to tactile stimuli, evidence of generalized hypersensitivity to visual, auditory, and olfactory stimuli has also been observed in FM patients (10,21–24). Given that FM patients appear to be hypersensitive to different types of sensory stimuli, we hypothesized that this increased sensitivity in response to noxious stimuli may partly reflect a more generalized hypersensitivity to salient sensory events. Thus, we implemented an analysis approach to evaluate the distinct brain responses to evoked pain onset and offset, which are 2 salient sensory events with opposing hedonic value. We reasoned that heightened responses to both pain onset and pain offset would support the view of a generalized hypersensitivity to salient stimuli in FM. Moreover, given that FM patients tend to report higher levels of negative affect, particularly pain catastrophizing, compared to controls, we hypothesized that exaggerated brain responses to pain onset/offset in FM would be positively associated with pain catastrophizing.

PATIENTS AND METHODS

Subject characteristics. A total of 53 FM patients (mean ± SD age 46.3 ± 11.4 years) and 17 control subjects (mean ± SD age 44.1 ± 14.8 years) initially entered the study. Each subject provided written informed consent prior to commencement of the study, and all study procedures were approved by the local institutional review board. Inclusion criteria included an age of ≥18 years and a diagnosis of FM by a rheumatologist for ≥1 year according to the American College of Rheumatology 2010 classification criteria for FM (2). Exclusion criteria included a history of psychiatric, neurologic, or autoimmune disorders; cardiac events and/or head injury; claustrophobia or magnetic resonance imaging (MRI) contraindication; current recreational drug use, including opioids; and pregnancy or plans to become pregnant. Patients were instructed to continue their medication regimens throughout the course of the study, which included antidepressants, gabapentin, nonsteroidal antiinflammatory drugs, and/or acetaminophen. Healthy control subjects were frequency-matched with the FM patients for age and sex.

It should be mentioned that while the number of control subjects in the present investigation is typical for group comparisons in functional MRI (fMRI) studies, we have elected to include a significantly larger number of FM patients. This unbalanced design was adopted to maximize statistical power and dynamic range for regression analyses evaluating the association between brain activations and behavioral variables within the patient group (see below), thereby enhancing our ability to understand the clinical significance of the functional changes observed across groups, as demonstrated in previous studies (19,25).

Experimental design and procedures. In our previous study (25), we examined brain responses to the prolonged painful cuff stimulation period, as well as the 15-second post-stimulus offset period to model painful after-sensations in the same sample of FM patients and controls. In contrast, in the present study, we investigated brain response to cuff stimulus onset and offset, both rapid transitory events, in order to examine the degree to which FM patients are hypersensitive to salient sensory stimuli represented by pain onset (cuff inflation) and pain offset (cuff deflation).

Subjects participated in a behavioral visit performed at Brigham and Women's Hospital and an MRI visit held at Athinoula A. Martinos Center for Biomedical Imaging. At the behavioral visit, subjects were asked to rate the severity and extent of their pain using a numerical rating scale (NRS) followed by administration of the Brief Pain Inventory (26), Neuropathic Pain Questionnaire (27), Widespread Pain Inventory, Symptom Severity Index (2), Pain Catastrophizing Scale (PCS) (28), Beck Depression Inventory (29), and a verbal anxiety NRS. Given the significant association between PCS scores and perceptual differences in painful after-sensations in FM patients that was previously reported by our group (25), we focused on the PCS to further evaluate the role between catastrophizing and brain processing of salient aspects of the painful stimulation (i.e., pain onset/offset).

Upon completion of self-report measures, subjects underwent QST, which included a cuff pain threshold assessment. Each subject's cuff pain threshold was individually determined using cuff pain algometry with an E20 Rapid Cuff Inflation System (Hokanson), which was adapted to inflate (i.e., reach the target pressures) and deflate (i.e., return to baseline) in ~2 seconds, in order to minimize the risk of startling the participants. For cuff pain threshold assessment, a 13 × 85 centimeter wide vascular pressure cuff was placed around the subject's left calf and secured with a Velcro strap. The cuff was connected to the E20 device and inflated to a pressure (mm Hg) individually calibrated to elicit a target pain intensity rating of ~40 on a 100-point scale

ranging from a score of 0 (indicating no pain) to100 (indicating worst pain imaginable). The pressure at which the subject rated a pain intensity of 40 on a 100-point scale was then used during the MRI cuff pain paradigm.

MRI acquisition, preprocessing, and statistical analyses. Functional MRI data were acquired using a 3T Siemens Tim Trio scanner equipped with a 32-channel head coil (Siemens Healthcare). A high-resolution structural scan was collected using a multiecho magnetization-prepared rapid gradient-echo pulse sequence (repetition time [TR] 2.53 seconds, echo time [TE] of TE1 1.64 msec, TE2 3.5 msec, TE3 5.36 msec, and TE4 7.22 msec, flip angle 7°, voxel size 1 × 1 × 1 mm). A T2*-weighted echo-planar image pulse sequence was also used to obtain high-resolution functional images during the cuff pain paradigm (TR 2 seconds, TE 30 msec, 37 slices, voxel size 3.1 × 3.1 × 3.6 mm). A total of 4 blood oxygen level–dependent (BOLD) runs were acquired (25). For each run, 2 block cuff pressure pain stimuli were delivered at the pressure previously determined during the threshold assessment procedure. The cuff pressure stimuli were delivered with a variable duration (75–105 seconds with a mean ± SD duration of 90 ± 10 seconds) to limit predictability. Following the end of each run, subjects were asked to rate the average pain intensity and unpleasantness of the stimulus using the NRS.

Functional MRI data preprocessing and analyses was performed with fMRI Expert Analysis Tool (FEAT; version 6), part of the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (www.fmrib.ox.ac.uk/fsl). Our imaging pipeline included slice timing (slicetimer) followed by motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT) (30), skull stripping using FMRIB Software Library's brain extraction tool (BET) (31), realignment of mean fMRI volume with FLIRT (30,32), grand mean intensity normalization by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight-line fitting [σ = 136–164 seconds depending on the run, estimated using cutoffcalc]), and spatial smoothing with a full-width half-maximum of 5 mm. Time-series statistical analysis was conducted using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (33). Cortical surface reconstruction was performed using FreeSurfer software (bbregister tool) for improved structural/functional coregistration purposes (34).

A within-subject analysis using a general linear model was performed by modeling the stimulus onset and offset transients as stick functions (35–37), each lasting a single TR in duration, corresponding to the approximate time of the cuff inflation and deflation (i.e., 2 seconds). In addition, the sustained tonic response between the onset and the offset periods was modeled as a boxcar function and designated as a regressor of no interest in the design matrix, lasting 75–105 seconds in duration. The model also included the 15-second post-stimulus period after stimulus offset, which we previously used to evaluate brain activity associated with painful after-sensations (25). All regressors were convolved with a canonical double-gamma hemodynamic response function (HRF). To minimize the effect of motion in our estimates of brain responses to pain onsets and pain offsets, the 6 head motion parameters (6 translations and 6 rotations), as well as a regressor of no interest for each volume determined to be an outlier in terms of motion (computed using fsl_motions_outliers), were entered into the design matrix. Time points within each run were flagged as outliers if they were deemed to have been significantly affected by motion based on the root mean square frame displacement (38), as performed in our previous study (25).

The relatively conservative approach of scrubbing motion outliers was used given our specific focus on stimulus onset and offset, transition phases that might be particularly vulnerable to stimulus-correlated motion. However, group comparisons revealed no significant differences in head motion (25). The resulting first-level parameter estimates and variance maps were registered to the Montreal Neurological Institute (MNI) 152 standard space using FMRIB's Non-linear Image Registration Tool (FNIRT) (39). Group maps were generated for the cuff pain onset and offset periods using a series of whole-brain voxelwise general linear models with FMRIB's Local Analysis of Mixed Effects (FLAME) 1+2 (40) and enabled automatic outlier detection enabled. The use of FLAME 1+2 is well suited for unbalanced designs such as this one because of its ability to model different variances using Metropolis–Hastings Markov chain Monte Carlo sampling (41,42) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/UserGuide). Statistical maps were cluster-corrected for multiple comparisons using FMRIB Software Library's default cluster-forming voxelwise threshold ($Z > 2.3$) and a corrected cluster significance threshold ($P < 0.05$).

Given that comparisons of pain onset and pain offset yielded significant differences in FM patients compared to controls (with significantly higher pain onset/offset effects in overlapping regions of the brain in FM patients), we generated an intersection mask of both contrast maps and parcellated it using anatomic labels derived from the Harvard Oxford Atlas in the FMRIB Software Library. Using an arbitrary threshold of 30, this parcellation method resulted in 5 subregions, which included the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), precentral gyrus (PrCG), and frontal pole (FP). These subregions were used as masks to extract and display percent signal change and time courses for illustrative purposes. To calculate percent signal change, the contrasts for parameter estimates from the onset and offset phases for each subject, along with the peak-peak height of the regressor and the mean of the functional time series data, were extracted from each voxel within our masks for each subject and averaged within groups. To visualize differences in percent signal change between groups for each mask, bar graphs were created to display the mean ± SEM for cuff pain onset and offset.

Table 1. Demographic, clinical, and psychosocial characteristics of the study cohort*

Variable	Healthy controls (n = 15)	Fibromyalgia patients (n = 38)	*P*
Age, years	45.53 ± 12.40	46.13 ± 13.44	0.882
PCS score, 0–52 scale	5.93 ± 5.97	23.16 ± 13.08	<0.001
CPA threshold	190.67 ± 85.81	101.18 ± 57.20	<0.001
NRS score, 0–100 scale	42.54 ± 3.82	44.84 ± 7.70	0.309

* Values are the mean ± SD. PCS = Pain Catastrophizing Scale; CPA = cuff pressure algometry; NRS = numerical rating scale.

Additionally, Pearson's 2-tailed bivariate correlational analyses were performed in patients between percent signal change values obtained from each of the aforementioned 5 masks (i.e., DLPFC, VLPFC, OFC, PrCG, and the FP) for onset, offset, and PCS scores. Lastly, given that salience can be determined both by the intensity of a stimulation as well as its painfulness, we performed an additional series of within-group exploratory correlational analyses via Pearson's 2-tailed correlation coefficient test between percent signal change values extracted from each of the 5 masked subregions during both onset and offset, cuff pressure levels (mm Hg), and pain ratings. Since these were not planned comparisons, but instead post hoc adjunctive correlational analyses, correction for multiple comparisons was not performed.

RESULTS

A total of 43 FM patients and 15 controls participated in the fMRI visit. Five subjects were excluded from analyses due to either technical difficulties encountered during scanning,

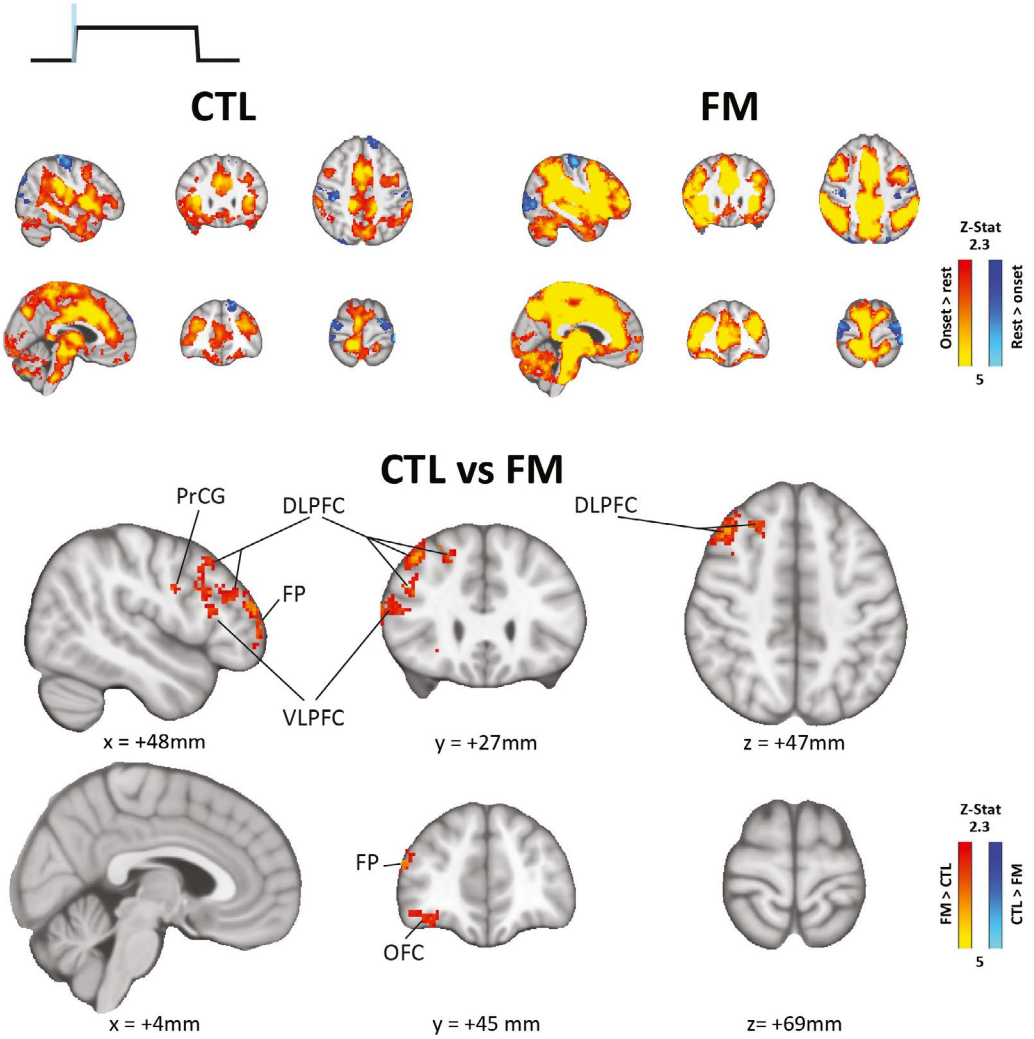

Figure 1. Statistical maps showing within-group brain responses to cuff pain onset for healthy controls (CTL) and fibromyalgia (FM) patients (top), with the group difference map indicating enhanced activation in several brain regions in FM patients compared to healthy controls (bottom). Increased brain activity in response to pain onset in the frontal cortical areas was observed in FM patients compared to controls, including in the dorsolateral prefrontal cortex (DLPFC), ventrolateral PFC (VLPFC), orbitofrontal cortex (OFC), precentral gyrus (PrCG), and frontal pole (FP).

incorrect scan parameters used, incomplete scan sessions, and in one case, due to a subject falling asleep during scanning. Therefore, the final sample for all subsequent analyses consisted of 38 FM patients (mean ± SD age 46.1 ± 13.4 years; 33 women) and 15 healthy controls (mean ± SD age 45.5 ± 12.4 years; 10 women). Demographic and behavioral data from the final sample of FM patients and controls are shown in Table 1. As expected and previously reported (25), the pressure required to elicit comparable pain ratings was significantly lower in FM patients compared to controls.

Functional MRI response to pain onset and offset. During cuff pain onset, both groups showed widespread increases in BOLD signaling, including in the primary somatosensory/motor (S1/M1; leg area), secondary somatosensory (S2), anterior and posterior insular, posterior parietal, pregenual anterior, middle and posterior cingulate, and lateral and medial prefrontal cortices, as well as in the cerebellum, basal ganglia, thalamus, and brainstem. Both groups also showed deactivation in S1/M1 (outside of the leg area) and higher-order visual cortices (e.g., lateral occipital cortex) (Figure 1).

Results from the whole-brain voxelwise group comparison analyses demonstrated that in response to cuff pain onset, FM patients (relative to controls) showed significantly greater activation in the frontal cortex, including the VLPFC (i.e., the inferior frontal gyrus), DLPFC (i.e., middle and superior frontal gyri), OFC, PrCG, and FP (see Table 2 for cluster information).

During pain offset, activations were demonstrated in both groups in the S2 anterior and posterior insulae and anterior middle cingulate cortices and in the basal ganglia, thalamus, and brainstem, with deactivations observed in the S1/M1 area (outside of the leg representation) and in the occipital, medial prefrontal, and dorsolateral prefrontal cortices (Figure 2). For FM patients, in response to stimulus offset, elevated BOLD signaling was demonstrated in the frontal cortex, including the DLPFC, VLPFC, OFC, PrCG, and FP, compared to healthy controls. Relative to controls, greater BOLD signal increases were seen in FM patients in regions not statistically significant in the onset contrast, including the dorsomedial prefrontal cortex, supplementary motor area, paracentral lobule, posterior cingulate gyrus, precuneus, posterior parietal cortex, fusiform and lingual gyri, middle temporal gyrus, bilateral thalamus, caudate nuclei, and cerebellum (see Table 2 for cluster information).

While the contrast maps for both pain onset and offset demonstrated that activation of several brain regions—including the DLPFC, VLPFC, OFC, PrCG, and FP—were each significantly enhanced in FM patients compared to healthy controls (Figures 3A and B), we found that such group differences were driven by variations in the activity patterns in the 2 phases. In response to the stimulus onset, both groups generally responded with activations in these regions, which were larger in FM patients (Figure 3C). During stimulus offset, however, activations were demonstrated in regions in FM patients in which deactivations were demonstrated in healthy controls

Table 2. Group differences in brain responses to pain onset and offset*

	Cluster size, no. of voxels	*P*	Z statistic	Peak		
				X	Y	Z
Pain onset						
FM patients > healthy controls						
R MFG	1,397	0.000404	4.41	42	14	36
R SFG			4.32	24	28	50
R MFG			4.17	40	26	46
R IFG			3.64	60	18	18
R FP			3.57	48	48	14
R PrCG			3.58	48	0	28
R OFG			3.29	28	32	−8
Pain offset						
FM patients > healthy controls						
R precuneus	17,067	1.79×10^{-23}	4.97	8	−76	48
R SFG			4.87	24	10	48
L PrCG			4.84	−2	−16	58
R FP			4.72	50	44	16
R OFG			3.71	32	40	−8
R MTG	8,567	1.63×10^{-14}	4.72	56	−48	−10
L fusiform gyrus			4.7	−20	−90	−20
L lingual/parahippocampal gyrus			3.25	−30	−46	−6
L thalamus	1,711	0.000212	4.45	−14	−6	14
R PCG			4.22	4	−50	10

* No significant group differences in brain responses to pain offset or onset were observed in healthy controls. FM = fibromyalgia; MFG = middle frontal gyrus; SFG = superior frontal gyrus; IFG = inferior frontal gyrus; FP = frontal pole; PrCG = precentral gyrus; OFG = orbital frontal gyrus; MTG = middle temporal gyrus; PCG = posterior cingulate gyrus.

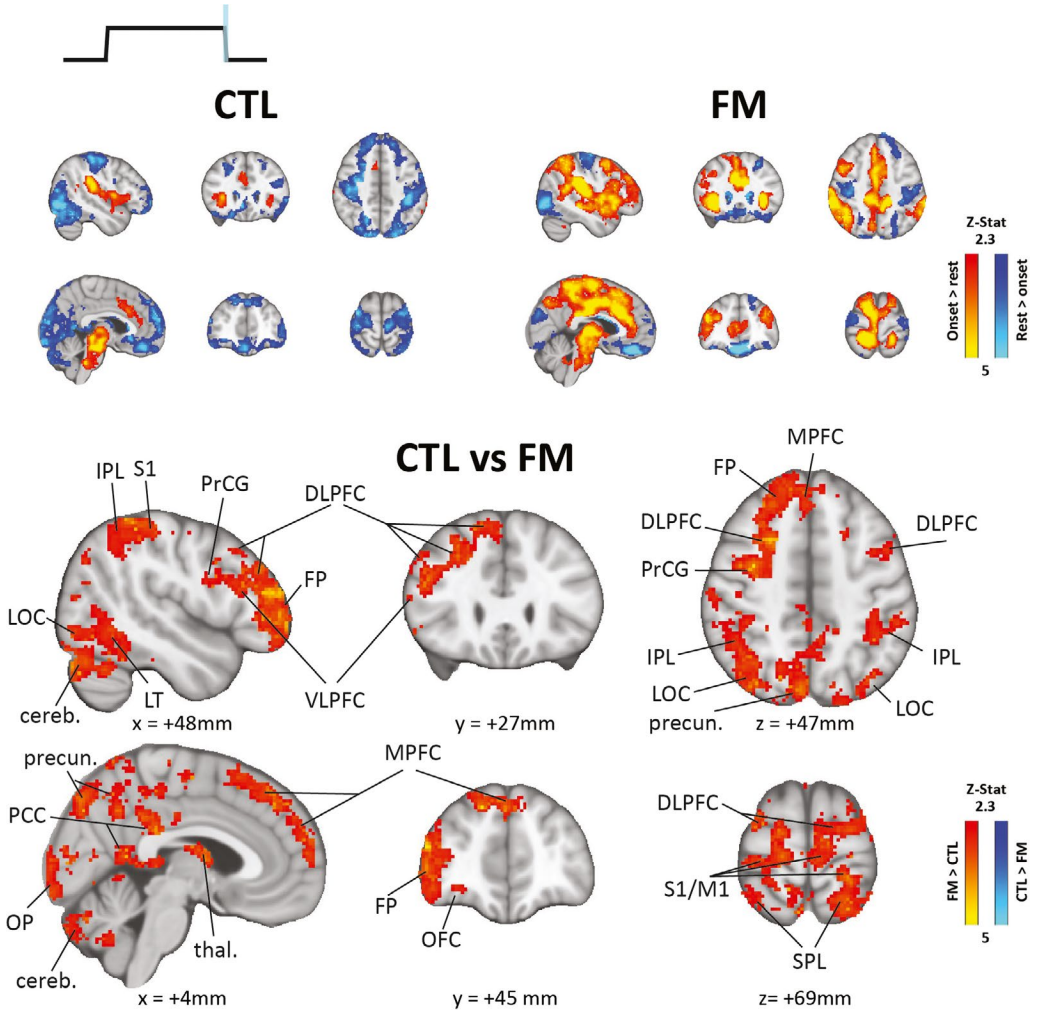

Figure 2. Statistical maps illustrating within-group brain responses to cuff pain offset for healthy controls and FM patients (top), with the group difference map displaying the contrast of enhanced activation in the brain regions of FM patients compared to healthy controls (bottom). Increased brain activity in response to pain offset in the lateral prefrontal cortical areas was observed in FM patients compared to controls, including in the DLPFC, VLPFC, OFC, PrCG, and FP. cereb. = cerebellum; LOC = lateral occipital cortex; IPL = inferior parietal lobule; S1 = primary somatosensory cortex; LT = lateral temporal cortex; precun. = precuneus; MPFC = medial prefrontal cortex; OP = occipital pole; PCC = posterior cingulate cortex; thal. = thalamus; M1 = primary motor cortex; SPL = superior parietal lobule (see Figure 1 for other definitions).

(Figure 3D). Examination of the time courses extracted from these regions revealed marked differences in neural response patterns between groups (Figure 3E). The most striking effect among the regions evaluated was the observed increases in BOLD signaling at the termination of cuff pain in the DLPFC, VLPFC, PrCG, and FP in FM patients compared to controls.

Correlational analyses. Results from the correlational analysis revealed a significant positive association between PCS scores and DLPFC signal changes during pain offset in FM patients (r = 0.33, P = 0.04) (Figure 4A). There was a trend toward a significant positive association between PCS scores and FP signal changes during pain offset as well (r = 0.30, P = 0.07). No other correlations with PCS reached statistical significance (P > 0.07).

Correlational analyses revealed no significant associations between brain response to cuff onset and cuff pressure in FM patients or controls. During cuff offset, however, we observed significant negative correlations between cuff pressure and activation in the OFC (r = –0.35, P = 0.03) and PrCG (r = –0.39, P = 0.02) in FM patients only (Figures 4B and C). No significant relationship between pain intensity ratings and brain response to cuff onset or offset in either group emerged, although there was a trend toward an association between pain intensity and PrCG activation at cuff onset (r = 0.31, P = 0.06). There was a significant positive correlation between pain unpleasantness ratings and VLPFC activity in patients during cuff onset (r = 0.35, P = 0.03) (Figure 4D) whereas in controls, there was a positive correlation between pain unpleasantness and VLPFC activation during cuff offset (r = 0.6, P = 0.02).

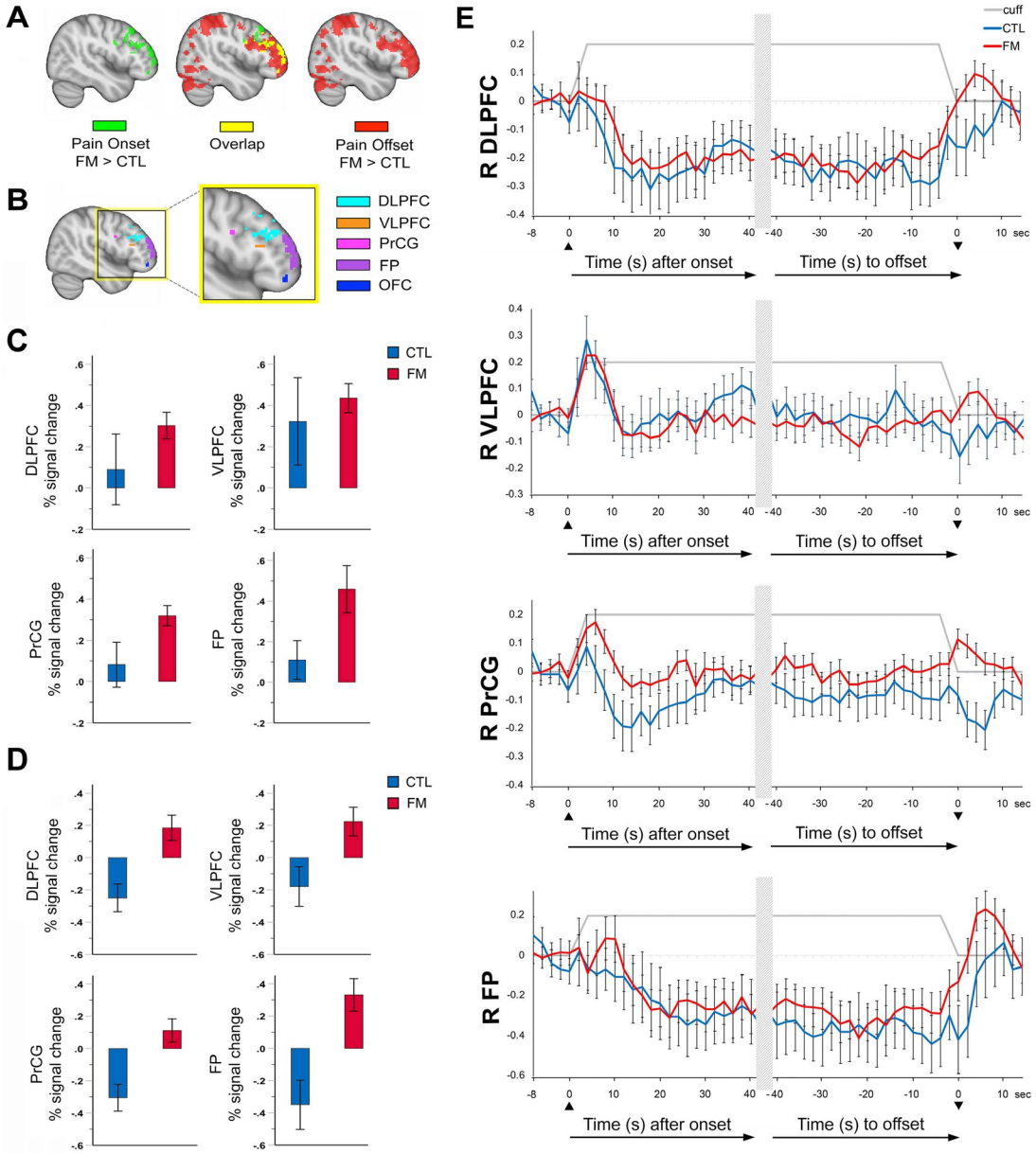

Figure 3. Group contrasts of pain onset and offset in various brain regions in FM patients compared to healthy controls showing shared regions of heightened response in the lateral PFC (LPFC) and in derived region of interest (ROI) masks. **A**, Statistical maps showing group differences in brain responses for FM patients compared to healthy controls during pain onset and pain offset, with overlapping regions common to both groups indicated. **B**, ROI masks included the DLPFC, VLPFC, PrCG, FP, and OFC. **C**, Mean percent signal changes extracted for anatomically parcellated ROIs created from the intersection mask for pain onset, including the DLPFC, VLPFC, PrCG, and FP. **D**, Mean percent signal changes extracted for anatomically parcellated ROIs (DLPFC, VLPFC, PrCG, and FP) created from the intersection mask for pain offset. **E**, Time courses for extracted blood-oxygenation level–dependent signal responses from anatomically parcellated subregions derived from the LPFC intersection mask for pain onset and offset. Values are the mean ± SEM. See Figure 1 for other definitions.

DISCUSSION

Our findings demonstrated that patients with FM, compared to controls, show extensive brain hyperactivity in response to both cuff pain onset and offset. While an increased response to pain onset was expected, particularly given the extensive literature demonstrating overall stronger brain responses to pain stimuli in FM, the large group differences observed at pain offset were striking. Such differences were noted in frontal regions that were also differentiated between FM patients and controls for pain onset (i.e., DLPFC, VLPFC, OFC, PrCG, and FP) as well as additional parietal, temporal, and occipital areas. Not only were group differences at offset more widespread than at onset, they reflected different activation/deactivation patterns—during offset, significant activations

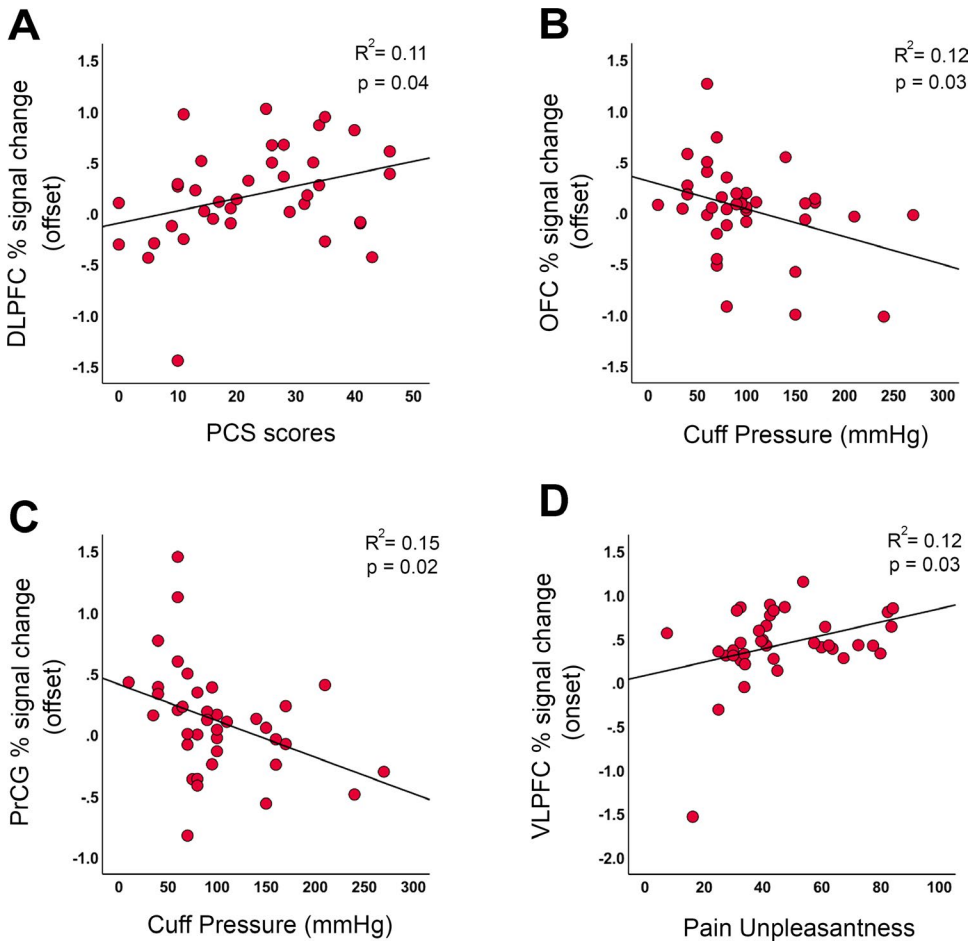

Figure 4. Scatterplots depicting correlations between brain activations extracted from anatomically parcellated regions of interest (ROIs) created from the intersection mask for pain onset and offset and pain catastrophizing scale (PCS) scores, cuff pressure (mm Hg), and pain unpleasantness ratings in FM patients only. **A**–**C**, DLPFC percent signal change in response to pain offset was positively correlated with PCS scores (**A**), and OFC (**B**) and PrCG (**C**) percent signal change in response to pain offset were negatively correlated with cuff pressure. **D**, VLPFC percent signal change in response to pain onset was demonstrated to be positively correlated with ratings of pain unpleasantness. See Figure 1 for other definitions.

in many regions were demonstrated in FM patients whereas deactivations were exhibited in healthy controls. Moreover, the magnitude of such hyperresponsiveness in FM patients was rather remarkable, particularly considering that intensity of stimuli presented to this group was 37.5% less than that for controls (mean ± SD 100 ± 43 mm Hg in FM patients and 160 ± 74 mm Hg in controls [25]), due to individualized calibration of the stimulus to achieve a pain intensity rating of ~40 on a 100-point scale.

Because increased brain responses to both onset (i.e., the event signaling the beginning of pain) and offset (i.e., its termination) were demonstrated in FM patients, our results are compatible with the notion that FM patients might generally be more sensitive to salient events (although this interpretation awaits proper corroboration with behavioral data). Several studies have reported a generalized increased sensitivity to non-noxious and non-somatic sensations, including auditory, gustatory, and olfactory stimuli (21–24). For instance, when presented with intense auditory stimuli of varying intensities, shorter auditory evoked potential (N1 and P2) latencies were demonstrated in FM patients compared to controls (24). Other studies using self-report questionnaires have demonstrated that FM patients tend to report greater sensitivity to everyday sounds and smells than their non-FM counterparts (22,23). Altogether, results from these studies, as well as our own demonstration of brain hyperresponsiveness to both cuff pain onset and offset, suggest that increased pain-related brain activity often reported in FM studies might perhaps reflect a more generalized hypersensitivity to salient aspects of the pain stimuli, rather than (or in addition to) their painful quality per se.

In addition, the positive association between pain unpleasantness ratings and VLPFC activation during cuff onset in FM patients may hint at dysregulated modulatory processing in regard to perceived controllability over pain in FM patients, given that a few studies have demonstrated greater VLPFC-related activity during self-controlled, painful stimulation (43) and less perceived pain during uncontrollable pain conditions, compared to controllable pain conditions, in healthy subjects (44).

Clinically, these results would support the use of cognitive and behavioral interventions focused on training salience detection/stimulus–driven orienting of attention, such as mindfulness meditation (45).

A notable finding gleaned from the present study is that FM patients showed frontal hyperresponsiveness to both cuff pain onset and offset compared to controls, particularly in the lateral PFC. The lateral PFC comprises multiple brain regions that work together to integrate cognitive inhibitory control functions and regulatory processes associated with threat detection (46,47). There is growing evidence that augmented activity in the lateral PFC, and the DLPFC in particular, may be associated with increased sensitivity to painful and non-painful somatic stimuli, perhaps indicative of impaired somatosensory gating in these patients (10,48).

While our data may be compatible with the hypothesis of dysregulation of salience detection, it should be noted that we did not observe group differences in canonical salience network nodes, such as the dorsal ACC or anterior insula, but rather, both groups showed similar levels of activations in these regions. Our findings warrant further investigation to determine the mechanism underlying PFC hyperactivation in FM, and whether this is driven by an overactivity in salience-related circuitry and/or an inability to sufficiently regulate/dampen these responses. Alternate explanations for greater prefrontal activation in response to stimulus onset/offset may correspond to a slower hemodynamic response recovery at offset (i.e., aberrant neurovascular coupling) and/or disruption in top-down control mechanisms, including greater catastrophizing or altered stimulus appraisal.

Another key finding was the significant positive association between pain catastrophizing and BOLD signal response in the DLPFC during cuff pain offset in FM patients. It is well understood that catastrophizing is an important contributing factor to the experience and expression of pain as well as its progression into persistent pain (49,50). Indeed, patients who tend to catastrophize about their pain report overall greater pain severity, rating higher in pain intensity and unpleasantness, than those patients who tend to not catastrophize (23). Moreover, the degree of catastrophizing has been shown to be predictive of whether or not an acute pain event actually develops into a chronic pain state (51). However, much less is known about the neurobiologic mechanism that drives this phenomenon. Our recent studies have shown that in patients with chronic pain, engaging in catastrophizing thoughts about clinical pain activates medial prefrontal and posterior cingulate cortices (52), though different circuits may support how catastrophizing influences perception of evoked pain in these patients. One theory posited is that catastrophizers are unable to disengage attention away from their pain and direct more attentional resources toward non-painful or salient stimuli encountered in their environment. This attentional bias, over time, may sensitize the system, overwhelming it to the point to which it can no longer compensate via descending inhibitory pathways. This, in turn, could lead to a host of pathologic downstream effects, including but not limited to pain amplification (hyperalgesia), the development of allodynic responses to previously innocuous signals, and/or a generalized hypersensitivity manifest across multiple sensory modalities. Our previous study showed that greater PCS scores were associated with greater connectivity between somatosensory (i.e., S1) and salience (i.e., anterior insula) processing regions during sustained evoked pain, which was compared to a resting state elevated S1–insula connectivity (53,54).

A confluence of evidence also points to the DLPFC as a possible candidate region responsible for driving this interaction, given its involvement in cognitive inhibitory control functions and attentional processes related to pain perception, as well as the detection and mediation of adaptive behavioral responses to aversive threats exhibited in this region (55). Our data provide support for this theory by demonstrating a significant association between DLPFC activity and catastrophizing during cuff pain offset in FM patients, suggesting that the tendency to catastrophize may be linked to an inability to appropriately disengage attention away from the salient sensory event—in this case, the termination of the cuff pain stimulus—despite the fact that the stimulus has ended and is therefore no longer noxious or threatening.

Other neuroimaging studies have reported findings that are consistent with our results. For example, Gracely and colleagues found that FM patients with high catastrophizing showed greater DLPFC activity during pain perception, a finding that persisted even when statistically controlling for depressive symptoms (56). Ellingson et al reported a significant positive correlation between catastrophizing, pain ratings, and DLPFC signal responses in FM patients, but not performance, during a cognitive attention/distraction task (Stroop task) (57). Specifically, the ability of FM patients to modulate their pain was impaired and varied depending on the degree of catastrophizing reported, and the magnitude of this relationship was linked to DLPFC signal responding—greater DLPFC activity was demonstrated in patients with higher catastrophizing. One interpretation suggested by Ellingson et al was that catastrophizing likely interferes with the pain modulatory system via descending pathways arising from the DLPFC, by weakening engagement of attentional resources to inhibit incoming nociceptive signals. Our result, in the context of their findings, provides further support for this theory, although more research is needed.

Several limitations should be considered when interpreting the present findings. First, given that our study utilized a cross-sectional design, drawing predictive conclusions (with regard to the relationship between brain response to cuff pain offset and the degree of pain catastrophizing) is not possible. Future studies employing a longitudinal design to investigate the causal nature of these relationships are needed. Second, medication usage was not controlled. Some patients were undergoing antidepressant therapy or receiving analgesics (gabapentin, nonsteroidal antiinflammatory drugs, and/or acetaminophen). As such, it is unclear to what extent medication might have affected

our results. Moreover, it remains to be determined whether the patterns of hyperactivation observed in FM patients can also be observed in other groups, including pain-free participants with similarly elevated levels of catastrophizing. Unfortunately, we were unable to evaluate the effects of PCS on BOLD signaling in our control participants as the dynamic range in their PCS scores was too narrow. Lastly, due to the secondary nature of this study, we did not collect behavioral data directly measuring salience, and our interpretation about differences in salience detection is only speculative at this point and will need to be confirmed in future investigations.

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. Loggia 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. Kim, Edwards, Napadow, Loggia.
Acquisition of data. Cahalan, Kim, Loggia.
Analysis and interpretation of data. Hubbard, Lazaridou, Cahalan, Kim, Edwards, Napadow, Loggia.

REFERENCES

1. Clauw DJ. Fibromyalgia: a clinical review. JAMA 2014;311: 1547–55.
2. 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.
3. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
4. Harris RE, Clauw DJ. How do we know that the pain in fibromyalgia is "real"? Curr Pain Headache Rep 2006;10:403–7.
5. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol 2007;26:465–73.
6. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–91.
7. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain 2013;154:2310–6.
8. Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013;136:1857–67.
9. López-Solà M, Woo CW, Pujol J, Deus J, Harrison BJ, Monfort J, et al. Towards a neurophysiological signature for fibromyalgia. Pain 2017;158:34–47.
10. Ceko M, Bushnell MC, Gracely RH. Neurobiology underlying fibromyalgia symptoms. Pain Res Treat 2012;2012:585419.
11. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295–302.
12. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70:41–51.
13. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.
14. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004;31:364–78.
15. Pujol J, López-Solà M, Ortiz H, Vilanova JC, Harrison BJ, Yücel M, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. PloS One 2009;4:e5224.
16. Williams DA, Gracely RH. Biology and therapy of fibromyalgia: functional magnetic resonance imaging findings in fibromyalgia [review]. Arthritis Res Ther 2006;8:224.
17. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcón GS, Mountz JM, Deutsch G. Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. Curr Rheumatol Rep 2000;2:141–8.
18. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Semin Arthritis Rheum 2014;44:68–75.
19. Loggia ML, Berna C, Kim J, Cahalan CM, Gollub RL, Wasan AD, et al. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. Arthritis Rheumatol 2014;66:203–12.
20. Albrecht DS, Forsberg A, Sandström A, Bergan C, Kadetoff D, Protsenko E, et al. Brain glial activation in fibromyalgia—a multi-site positron emission tomography investigation. Brain Behav Immun 2019;75:72–83.
21. Wilbarger JL, Cook DB. Multisensory hypersensitivity in women with fibromyalgia: implications for well being and intervention. Arch Phys Med Rehabil 2011;92:653–6.
22. Hollins M, Harper D, Gallagher S, Owings EW, Lim PF, Miller V, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215–21.
23. Geisser ME, Glass JM, Rajcevska LD, Clauw DJ, Williams DA, Kileny PR, et al. A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. J Pain 2008;9:417–22.
24. Carrillo-de-la-Peña MT, Vallet M, Pérez MI, Gómez-Perretta C. Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients: a test of the generalized hypervigilance hypothesis. J Pain 2006;7:480–7.
25. Schreiber KL, Loggia ML, Kim J, Cahalan CM, Napadow V, Edwards RR. Painful after-sensations in fibromyalgia are linked to catastrophizing and differences in brain response in the medial temporal lobe. J Pain 2017;18:855–67.
26. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133–7.
27. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29–36.
28. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995;7:524–32.
29. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100.
30. Jenkinson M, Bannister P, Brady JM, Smith SM. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;2:825–41.
31. Popescu V, Battaglini M, Hoogstrate WS, Verfaillie SC, Sluimer IC, van Schijndel RA, et al, on behalf of the MAGNIMS Study Group. Optimizing parameter choice for FSL-Brain Extraction Tool (BET) on 3D T1 images in multiple sclerosis. Neuroimage 2012;61:1484–94.
32. Jenkinson M, Smith SM. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5:143–56.

33. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 2001;14:1370–86.
34. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 2009;48:63–72.
35. Uludağ K. Transient and sustained BOLD responses to sustained visual stimulation. Magn Reson Imaging 2008;26:863–9.
36. Becerra L, Navratilova E, Porreca F, Borsook D. Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans. J Neurophysiol 2013;110:1221–6.
37. Konishi S, Donaldson DI, Buckner RL. Transient activation during block transition. Neuroimage 2001;13:364–74.
38. Jenkinson M. Measuring transformation error by RMS deviation: FMRIB technical report TR99MJ1. URL: https://www.fmrib.ox.ac.uk/datasets/techrep/tr99mj1/tr99mj1.pdf.
39. Andersson JL, Jenkinson M, Smith S. Non-linear registration aka spatial normalisation: FMRIB technical report TR07JA2. 2007. URL: https://www.fmrib.ox.ac.uk/datasets/techrep/tr07ja2/tr07ja2.pdf.
40. Beckmann CF, Jenkinson M, Smith SM. General multi-level linear modelling for group analysis in FMRI: FMRIB technical report TR01CB1. URL: https://www.fmrib.ox.ac.uk/datasets/techrep/tr01cb1/tr01cb1.pdf.
41. Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 2004;21:1732–47.
42. Mumford JA. A comprehensive review of group level model performance in the presence of heteroscedasticity: can a single model control Type I errors in the presence of outliers? Neuroimage 2017;147:658–68.
43. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. J Neurosci 2006;26:11501–9.
44. Salomons TV, Johnstone T, Backonja MM, Shackman AJ, Davidson RJ. Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex. J Cogn Neurosci 2007;19:993–1003.
45. 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.
46. Gray JR, Braver TS, Raichle ME. Integration of emotion and cognition in the lateral prefrontal cortex. Proc Nat Acad Sci U S A 2002;99:4115–20.
47. Peers PV, Simons JS, Lawrence AD. Prefrontal control of attention to threat. Front Hum Neurosci 2013;7:24.
48. 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.
49. Keefe FJ, Brown GK, Wallston KA, Caldwell DS. Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. Pain 1989;37:51–6.
50. Sullivan MJ, Stanish W, Waite H, Sullivan M, Tripp DA. Catastrophizing, pain, and disability in patients with soft-tissue injuries. Pain 1998;77:253–60.
51. Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. Spine (Phila Pa 1976) 1995;20:722–8.
52. Lee J, Protsenko E, Lazaridou A, Franceschelli O, Ellingsen DM, Mawla I, et al. Encoding of self-referential pain catastrophizing in the posterior cingulate cortex in fibromyalgia. Arthritis Rheumatol 2018;70:1308–18.
53. 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.
54. Kim J, Loggia ML, Edwards RR, Wasan AD, Gollub RL, Napadow V. Sustained deep-tissue pain alters functional brain connectivity. Pain 2013;154:1343–51.
55. Seminowicz DA, Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. J Pain 2017;18:1027–35.
56. 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.
57. Ellingson LD, Stegner AJ, Schwabacher IJ, Lindheimer JB, Cook DB. Catastrophizing interferes with cognitive modulation of pain in women with fibromyalgia. Pain Med 2018;19:2408–22.