Functional Imaging of Pain in Patients with Primary Fibromyalgia

DANE B. COOK, GUDRUN LANGE, DONALD S. CICCONE, WEN-CHING LIU, JASON STEFFENER, and BENJAMIN H. NATELSON

ABSTRACT. ***Objective.*** To examine the function of the nociceptive system in patients with fibromyalgia (FM) using functional magnetic resonance imaging (fMRI).

Methods. Two groups of women, 9 with FM and 9 pain-free, volunteered to participate. In Experiment 1, we assessed psychophysical responses to painful stimuli and prepared participants for fMRI testing. For Experiment 2, subjects underwent fMRI scanning while receiving painful and nonpainful heat stimuli. Conventional and functional MR images were acquired using a 1.5 T MR scanner. Scanning occurred over 5 conditions. Condition 1 served as a practice session (no stimuli). Conditions 2 and 5 consisted of nonpainful warm stimuli. Conditions 3 and 4 consisted of an absolute thermal pain stimulus (47°C) and a perceptually equivalent pain stimulus delivered in counterbalanced order.

Results. Experiment 1 indicated that subjects with FM were significantly more sensitive to experimental heat pain than controls ($p < 0.001$). In Experiment 2, fMRI data indicated that the FM group exhibited greater activity than controls over multiple brain regions in response to both nonpainful and painful stimuli ($p < 0.01$). Specifically, in response to nonpainful warm stimuli, FM subjects had significantly greater activity than controls in prefrontal, supplemental motor, insular, and anterior cingulate cortices ($p < 0.01$). In response to painful stimuli, FM subjects had greater activity in the contralateral insular cortex ($p < 0.01$). Data from the practice session indicated brain activity in pain-relevant areas for the FM group but not for controls.

Conclusion. Our results provide further evidence for a physiological explanation for FM pain. (J Rheumatol 2004;31:364–78)

Key Indexing Terms:
FIBROMYALGIA
MUSCULOSKELETAL PAIN
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Fibromyalgia (FM) is a condition characterized by widespread musculoskeletal pain and multiple tender point sites[1]. The etiology of the syndrome is unknown, and no consistent underlying mechanism has been identified. However, evidence of increased pain sensitivity and altered nociceptive processing in patients with FM suggests that dysregulation of the central nervous system (CNS) may be an important element underlying FM pain.

Results from studies examining sensitivity to experimentally induced pain have shown that patients with FM have lower pain thresholds and report higher pain ratings in response to pressure, heat, cold and electrical stimuli[2-6]. Experiments examining pain regulatory systems have shown patients with FM to display a dysregulation of diffuse noxious inhibitory controls[7,8], an exaggerated wind-up response to repetitive pain stimuli[9], and absence of an exercise-induced analgesic response[5,10]. Together, these results point to central dysregulation of the nociceptive system. However, one limitation of previous research examining nociceptive processes in FM has been the reliance on self-report measures of pain. Objective evidence of abnormal nociception is needed to better understand the pathophysiologic processes involved, and provide converging evidence of the patient's self-reported symptoms.

The emergence of brain imaging as an investigative tool has resulted in a greater understanding of the complexity of the nociceptive system in humans. Research using experimental pain stimuli (e.g., noxious heat, noxious chemicals, electricity), and employing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)

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techniques, has identified many of the brain areas involved in processing the nociceptive signal in healthy people. The areas most consistently implicated in pain processing, and thus considered pain-relevant, are the sensory cortex, prefrontal cortex, inferior parietal cortex, anterior cingulate cortex, insula, lentiform nucleus, and thalamus[11-16]. Moreover, improvements in behavioral research designs that control attention during scanning, examine painful versus nonpainful stimuli, and obtain pain intensity and affective ratings during stimulation have provided important information regarding the cognitive, sensory, and emotional processes that are inherently involved in the perception of pain[12,15,17-21].

Recently, 2 single-photon emission computed tomography (SPECT) studies in FM have reported reduced regional cerebral blood flow (rCBF) to the thalamus, heads of the caudate nucleus, and pontine tegmentum at rest[22,23]. These results are consistent with data obtained from other clinical pain populations (e.g., cancer pain, neuropathic pain, reflex sympathetic dystrophy, rheumatoid arthritis) and have been interpreted as an inability of the nociceptive system to modulate or compensate for the constant barrage of incoming nociceptive signals[24-27]. The results of these studies have provided important information regarding the resting state of the brain in chronic pain. To our knowledge, only one report exists using functional neuroimaging methods to assess how the brains of patients with FM respond to painful stimuli. In a well designed study, Gracely, *et al*[28] reported that fMRI brain responses to experimental pressure pain, set at either similar stimulus levels or similar subjective pain levels, were augmented in FM patients compared to controls. This finding supports the view that physiological processing of pain is altered in FM.

We used fMRI to examine neural activation patterns to experimental pain in patients with FM and healthy controls. We attempted to exploit recent improvements in fMRI research by controlling attention during scanning, using both painful and nonpainful stimuli, obtaining pain ratings during stimulation rather than after stimulus presentation, and controlling for perceptual differences in pain (stimulus) intensity. Our design as detailed in Table 1 was intended to test the following hypotheses: (1) presented with a nonpainful (warm) stimulus, FM patients will exhibit neural responses in brain regions associated with pain perception whereas controls will not; (2) presented with a painful (hot) stimulus of equal absolute magnitude, FM patients will exhibit greater neural responses in brain regions associated with pain perception compared to controls; (3) presented with a perceptually equivalent pain (hot) stimulus, FM patients and controls will display similar neural responses in brain regions associated with pain perception; and (4) neural responses to nonpainful (warm) stimuli will remain elevated in FM patients but not in controls following the presentation of several painful stimuli (i.e., fail to recover). If supported, the results would provide neurophysiological evidence of altered sensory processing and provide objective support for enhanced pain perception in patients with FM.

Table 1. Order of heat and pain stimuli during fMRI scanning.

Run	Condition	Description
1	Practice	Practice rating on the pain intensity scale; no stimulation
2	Random warm stimuli	5 random warm stimuli from 34˚C to 42˚C in 2˚ increments
3 and 4	Pain stimuli	Counterbalanced presentation of either 47˚C or pain previously rated as a 5 on the 0–10 scale
5	Random warm stimuli	5 random warm stimuli from 34˚C to 42˚C in 2˚ increments

MATERIALS AND METHODS

This study consisted of 2 separate experiments conducted about one week apart. Experiment 1 was intended to assess psychophysical responses to painful stimuli and to prepare the participants for subsequent fMRI testing. This included practice at rating painful and nonpainful heat stimuli using the same equipment used in the fMRI experiment, and establishing temperatures to be used during fMRI testing. For Experiment 2, participants reported to the MRI suite of the university hospital for fMRI data collection.

Subjects. Eighteen right handed females (n = 9 FM, n = 9 healthy controls) between the ages of 18 and 45 years volunteered to participate. All participants were recruited from a large patient pool through the CFS/FM Center. Patients met American College of Rheumatology criteria for FM[1] and had pain as their major symptom complaint. FM patients also met US Centers for Disease Control criteria for chronic fatigue syndrome[29]. Participants were screened to ensure that they were not claustrophobic or pregnant, and had no metal in the body. Participants were also screened to ensure that they were not taking anticonvulsant, antihypertensive, antidepressant, or pain medication for at least 3 weeks prior to the study. Additionally, participants were assessed using the Computerized Diagnostic Interview Schedule (Q-DIS)[30] to confirm they were free from Axis I psychiatric disorders that might affect pain ratings. Controls were healthy females, free from any current or lifetime Axis I psychiatric diagnosis, and not taking medication other than oral contraceptives. All participants signed an informed consent explaining the procedures of the study prior to testing.

Experiment 1

Procedures. Participants completed a battery of questionnaires including the Spielberger State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Kohn Reactivity Scale (KRS), and the short-form McGill Pain Questionnaire (MPQ)[31-34]. The STAI and BDI were used to assess anxiety and depression prior to testing, and to examine possible relationships between affect and pain ratings. We employed the KRS because of reports of hypervigilance in patients with FM that may affect responses to sensory testing[35]. The MPQ was employed to assess current pain and to examine the effect of chronic pain symptoms on acute pain ratings.

Sensory stimulation apparatus. Painful and nonpainful heat stimuli for all tests were delivered using a quantitative sensory testing unit (Medoc TSA-2001, Medoc Ltd., Ramat Yishai, Israel). Stimuli were delivered to the thenar eminence of the nondominant hand with a 300 mm^2 Peltier thermode, and using the WinTSA software provided by Medoc.

Threshold and suprathreshold testing. Heat and pain thresholds were assessed using the ascending method of limits. Baseline temperature for the thermode was kept at 32°C. The rate of temperature change was set to

increase at 1°C/s with a return to baseline rate of 10°C/s for both the warm threshold and pain threshold measurements.

Psychophysical responses to pain were assessed using 10 random suprathreshold heat stimuli. Each stimulus lasted 10 s with an interstimulus interval of 2 min. Temperatures ranged from 44.5°C to 49°C in 0.5°C increments. Stimuli were rated along 2 separate 0–10 category-ratio (CR-10) scales designed to measure both pain intensity and pain unpleasantness[36] (Figure 1). The CR-10 scales have been widely used in the study of pain and have been shown to be reliable and valid measures of pain ratings[37-41]. Moreover, the CR-10 scale with the specific placement of the verbal anchors was designed to combine the advantages of ratio-scaling techniques with those of simple rating methods, thus providing estimations of psychophysical growth functions while maintaining the ability to make interindividual comparisons[37]. A detailed description of the methods used to determine the psychophysical characteristics of the painful stimuli is provided in an Appendix. Immediately after the sensory testing session, the State Anxiety Inventory (SAI) form and MPQ were given to assess the level of anxiety provoked by testing and to describe the heat pain experienced during the testing session, respectively.

Experiment 2

Participants arrived at the MRI suite and completed the STAI, BDI, and MPQ for the same purpose as described in Experiment 1. Participants were then reacquainted with the CR-10 scales. Immediately prior to testing, subjects were reminded that they were about to receive a number of stimuli, some of which may be considered "extremely painful," but that no skin damage would result.

Imaging parameters. Conventional and fMRI image acquisitions were performed on a 1.5 T Echospeed Horizon MR scanner (GE, Milwaukee, WI, USA) using whole-body echoplanar imaging (EPI) with a whole-head transmit-receive coil. Foam cushions were used to immobilize the head within the coil to minimize motion degradation. The subjects wore MRI-compatible earmuffs for communication with the experimenter and to minimize scanner noise during acquisition. Subjects were then fitted with a set of fiber optic goggles (Avotec, Jensen Beach, FL, USA) for viewing the CR-10 scales (Appendix). Conventional acquisitions consisted of twenty-eight 5 mm thick T1 weighted [TR 450 ms, TE 20 ms, field of view (FOV) 24 cm] axial images with a matrix of 256 × 256. Functional MRI acquisitions were obtained with a gradient echo sequence and a spiral trajectory (TR 2000, TE 40) and consisted of twenty 5 mm thick slices. The acquisition matrix was 64 × 64 and FOV 20 cm^2, delivering an in-plane voxel resolution of 3.125 × 3.125 × 5 mm. The images were acquired at the same slice locations for subsequent overlays to correlate anatomic location with changes in fMRI signal intensity. The total experimental session, including fMRI and conventional MRI acquisitions, was roughly 40 min.

Experimental protocol. After T1 image acquisition, subjects were fitted with the thermode on the thenar eminence of the left hand. A toggle switch used to rate pain intensity and unpleasantness was placed in the right hand. The toggle switch consisted of a small dial (~10 mm diameter) that was easily moved with use of the subject's thumb and index finger. The amount of movement required to scroll the entire scale was less than 1 inch. Subjects were instructed not to move during the positioning of these devices.

Functional images were acquired over 5 separate runs using a boxcar design (Figure 2). Each run consisted of six 30 s off-periods (no stimulation) and five 10 s on-periods (heat stimuli) for a total of 230 s. The pain intensity scale was in view for the subject throughout the experimental protocol, and the pain unpleasantness scale was shown at the end of each run. The order and description of each condition is given in Table 1 and a depiction of the experiment design in Figure 2.

After functional MR data acquisition, the raw data were transferred to a remote Sun SPARC10 workstation through a dedicated Ethernet connection. The raw data were reconstructed offline using software developed under IDL (Interactive Data Language, Research Systems, Boulder, CO, USA). Due to the saturation effect, the first 3 functional images of each run were not used in statistical analyses. Images were realigned for motion correction, coregistered to the T1 anatomical image, and normalized to

PAIN INTENSITY SCALE		PAIN UNPLEASANTNESS SCALE	
0	NO PAIN AT ALL	●	UNBEARABLE
½	VERY FAINT PAIN (just noticeable)	10	EXTREMELY UNPLEASANT (almost unbearable)
1	WEAK PAIN	9	
2	MILD PAIN	8	
3	MODERATE PAIN	7	VERY UNPLEASANT
4	SOMEWHAT STRONG PAIN	6	
5	STRONG PAIN	5	UNPLEASANT
6		4	
7	VERY STRONG PAIN	3	MODERATELY UNPLEASANT
8		2	MILDLY UNPLEASANT
9		1	WEAKLY UNPLEASANT
10	EXTREMELY INTENSE PAIN (almost unbearable)	2	VERY FAINT UNPLEASANTNESS (just noticeable)
●	UNBEARABLE PAIN	0	NOT UNPLEASANT

Figure 1. Pain intensity and pain unpleasantness scales. Subjects viewed the pain intensity scale throughout each condition, while the pain unpleasantness scale was viewed immediately after each condition.

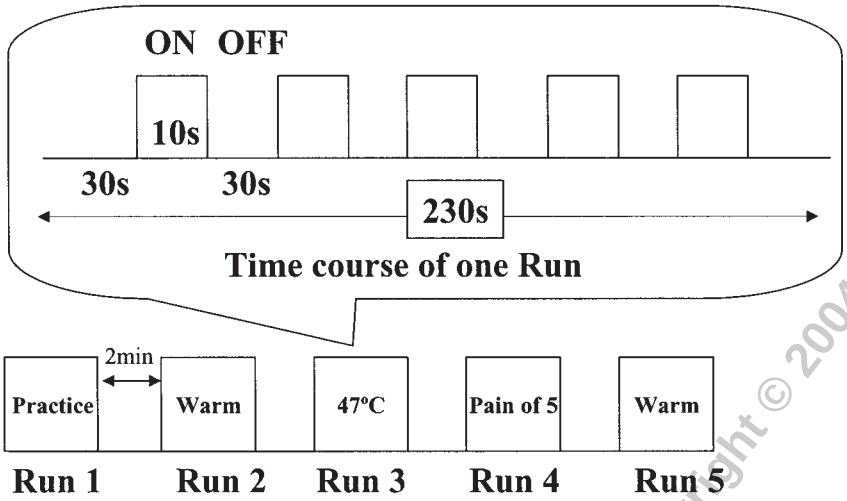

Figure 2. A graphic display of the experiment design used in this study. Each session consisted of 5 runs representing different conditions of the study. Each run lasted a total of 230 s and was divided into six 30 s "off-periods" and five 10 s "on-periods."

Talairach space using Statistical Parametric Mapping software (SPM99)[42]. The data were high-pass filtered with a 128 s cutoff period, low-pass filtered with an 8 s cutoff period, smoothed spatially (8 × 8 × 10 mm), and globally scaled to normalize the signal intensity. The maximum displacement was measured using the value (mm or degree) from the motion correction in x, y, z, roll, pitch, and yaw directions. Immediately after the fMRI testing session, the SAI and MPQ were given to assess the level of anxiety provoked by testing and to describe the heat pain experienced during the testing session, respectively.

Statistical analyses. For Experiment 1, subject characteristics, questionnaire data, thresholds, and peak ratings were analyzed using independent samples t tests with Bonferroni correction for multiple comparisons. Due to technical error or pain tolerance limitations, 4 subjects with FM did not receive the 48.5°C and 49°C stimuli, and therefore data analyses were performed on the 8 random stimuli that were administered to all participants. Ratings of pain intensity and unpleasantness for the 8 random heat stimuli were examined using a 2 group (FM and Control) × 8 temperature (44.5°C to 48°C) repeated measures analysis of variance. Analysis of covariance (ANCOVA) were used to examine main and interaction effects after parceling out the effects of selected potential confounding variables. Linear regression analysis and curve estimation was performed on natural log plots to describe the relationship between pain ratings and temperature for each group. When appropriate, effect sizes were calculated according to the method of Cohen[43]. Rough guidelines for Cohen's d are that 0.2 is small, 0.5 is moderate, and 0.8 is large. For Experiment 2, questionnaire data and unpleasantness ratings were examined using independent samples t tests. Pain intensity ratings during fMRI testing were examined using a 2 group × 5 temperature repeated measures ANOVA.

Analysis of the fMRI data was performed using SPM99 software[42]. First, single-subject analyses were performed by linear regression of the fMRI data. Within-group analyses were then conducted by examining the mean responses during each condition for the FM and control groups separately, using dependent samples t tests. The statistical activation maps were viewed using an uncorrected p value of 0.01. This voxel-based analysis searched the entire brain for areas that have been previously reported as pain-relevant. These regions included the somatosensory, motor, prefrontal, parietal, insular, and cingulate cortices, the thalamus, amygdala, and basal ganglia[11-16,22,23]. We then compared the FM and control groups using region of interest (ROI) analyses. These between-groups comparisons were restricted to pain-relevant regions that reached statistical significance in the within-group analyses. This process reduced the search volumes from > 100,000 voxels for the within-group analyses to less than 3000 voxels for the between-groups ROI analyses. This procedure reduced the probability of making a type II error by reducing the number of comparisons. The ROI analyses ($p < 0.01$, Bonferroni corrected) tested for differences between groups within pain-relevant areas after controlling for depressed mood (BDI scores) and chronic pain (MPQ total scores). Finally, regression analyses were used to determine the relationship between pain ratings during scanning and brain activity for the entire sample.

Since the heat stimulus was delivered to the left thenar eminence, contralateral activity represents right brain activity, while ipsilateral activity represents left brain activity. Locations, z-scores, and cluster values for Tables 2 and 3 represent the numbers observed for the maximal voxel within the gray matter of a given cluster. Table and text data are presented as mean ± SD and graphic data are presented as mean ± SE.

RESULTS

Experiment 1

Subject characteristics. There were no significant differences in the age, height, or weight of the 2 groups. FM participants were a mean age of 37 ± 5 years, height 163 ± 6 cm, and weight 67 ± 19 kg. Controls were a mean age 35 ± 3 years, height 163 ± 6 cm, and weight 65 ± 11 kg. Prior to testing, the FM participants reported more depressed mood (BDI scores: FM 8.4 ±7 vs controls 2.4 ±2; $t_{1,16} = 2.6$; $p = 0.02$), were more reactive (KRS scores: FM 87.6 ± 14 vs controls 66.3 ± 15; $t_{1,16} = 3.1$; $p = 0.007$), and were in more resting pain than controls (MPQ total: FM 10.3 ± 7 vs controls 0.7 ± 1; $t_{1,16} = 4.0$; $p = 0.001$). There were no significant differences in state or trait anxiety prior to testing.

Thresholds and peaks. There were no significant group differences for either the temperatures indicated as warm threshold (FM 33.3 ± 0.5°C vs controls 33.4 ± 0.7°C) or pain threshold (FM 43.5 ± 2.6°C vs controls 44.5 ± 3.4°C). The effect size for the difference in pain threshold temperature was moderate (ES d = 0.36). Peak pain intensity at 48°C

Table 2. Local maxima, z scores, cluster sizes, and associated gray matter regions expressed as Brodmann's classifications or anatomical region for the control group. Activations within the control group across conditions. Coordinates (x, y, z) represent the most significantly activated voxel based on the highest z score. Depending on the size of the cluster, several anatomical areas may be represented. Regions within each cluster were identified with locally developed software designed to examine each voxel within a cluster for its designated area based on Talairach coordinates.

Condition	Control Group				
	Local Max (x, y, z)	Z Score	Cluster Size (K_E)	Gray Matter Regions within the Clusters Left	Right
Practice	No significant areas			No significant regions	No significant regions
Random warm Stimuli #1	4 –18 12*	2.7	16	No significant regions	Thalamus
Pain: 47°C stimulus	42 –2 44**	3.6	25		BA 6
	–18 12 4**	3.4	16	Putamen	
	32 42 34**	3.2	13		BA 9
	20 16 –4**	3.0	13		Putamen
	–2 –16 10**	3.0	12		Thalamus
	20 2 36**	3.0	12		BA 24
	54 –30 48*	2.6	6		BA 2
	–30 34 28*	2.6	10	BA 9	
Pain: temperature rated as 5	40 16 –2**	3.7	15		Anterior insula
	62 –10 6**	3.5	141		BA 6, BA 40
	32 42 34*	2.9	15		BA 9
	–38 –22 10*	2.8	5	Anterior insula	
	–20 –24 42*	2.9	5	BA 31	
	–24 56 24*	2.8	3	BA 10	
Random warm stimuli #2	0 –58 40**	3.9	34	BA 7	BA 7
	40 34 18**	3.9	83		BA 10
	4 –28 2**	3.5	156	Thalamus	Thalamus
	8 –26 36**	3.3	54		BA 23, BA 24, BA 31
	4 –34 50**	3.2	18		BA 5
	10 14 40**	3.1	24		BA 32
	42 – 16 2*	2.8	11		Anterior insula

* $p \leq 0.005$, ** $p \leq 0.001$.

was significantly greater in the FM group compared to controls (FM 5.0 ± 2.8 vs controls 2.9 ± 1.2; p = 0.05). Peak pain unpleasantness at 48°C was not different between groups (FM 4.1 ± 2.8 vs controls 3.7 ± 2.3).

Suprathreshold pain testing. Pain intensity ratings for the 8 stimuli are presented in Figure 3. Repeated measures ANOVA revealed a significant group × temperature interaction ($F_{7,112} = 13.2$, $p < 0.001$] for pain intensity ratings. Linear regression of the log-transformed data revealed that for the control group each 0.5°C increase in temperature was associated with an 18% increase in pain intensity ratings. For the FM group each increase in temperature was associated with a 35% increase in pain intensity ratings. Thus, the FM group was almost twice as sensitive to painful heat stimuli as controls. Separate ANCOVA using the total score from the BDI and MPQ, respectively, failed to eliminate the interaction, suggesting that depression and resting pain did not explain the increased pain sensitivity observed in the FM group. There was neither significant main effects nor a significant interaction for pain unpleasantness ratings.

Post-test pain and anxiety. After pain testing, FM participants reported being significantly more anxious than controls (STAI scores: FM 30.2 ± 3 vs controls 25.2 ± 4; $t_{1,16} = 3.2$; p = 0.006). MPQ totals describing the heat pain experienced during testing were higher in the FM group (ES d = 0.64), but were not significantly different from controls (FM 8.3 ± 5.4 vs controls 5.6 ± 3.1; p = 0.09). This was likely due to the high variability within groups. Further analysis of pain descriptors indicated that the 3 most common adjectives used by both groups were "hot-burning," "sharp," and "tender." Thus, both FM and control participants used similar terms to describe the pain experience.

Experiment 2

Before testing, FM participants reported a more depressed mood (BDI scores: FM = 7.7 ± 7 vs controls 0.9 ± 1; $t_{1,16} = 2.9$; p = 0.01) and were in greater resting pain (MPQ total: FM 7.7 ± 6 vs controls 0.7 ± 1; $t_{1,16} = 3.5$; p = 0.003) compared to controls. There were no significant group differences in anxiety prior to scanning.

Functional imaging results. Significant blood oxygen level-dependent (BOLD) signal increases ($p < 0.01$) for each condition can be seen in Tables 2 (control group) and 3 (FM group). The combined results across all experimental conditions are illustrated in Figure 4.

Practice session (Condition 1): within-group analyses. SPM analysis indicated no significant areas of activation in the control group (Table 2); however, this was not the case for

the FM group (Table 3). Practice ratings and placement of the thermode on the hand resulted in significant activation bilaterally in the supplemental motor (BA 6), primary motor (BA 4), and sensory association (BA 5) cortices. Significant contralateral (right side) activity was observed in prefrontal (BA 9), superior parietal (BA 7), and posterior insular cortices. Ipsilateral activity was identified in the putamen.

Between-group analyses. The control group did not exhibit any significant activation during practice. Therefore, there were no comparisons to the FM group. T tests of the areas of activation for the FM group (FM – controls) indicated no significantly greater areas when compared to controls. Thus, while activity was observed in several pain-relevant areas in the FM group, these areas were not significantly greater than

Table 3. Local maxima, z scores, cluster sizes, and associated gray matter regions expressed as Brodmann's classifications or anatomical regions for the FM group. Activations within the control group across conditions. Coordinates (x, y, z) represent the most significantly activated voxel based on the highest z score. Depending on the size of the cluster, several anatomical areas may be represented. Regions within each cluster were identified with locally developed software designed to examine each voxel within a cluster for its designated area based on Talairach coordinates.

Condition	Local Max (x, y, z)	Z Score	Cluster Size (K_E)	FM Group Gray Matter Regions within the Clusters Left	Right
Practice	0 –34 76**	3.7	265	BA 4, BA 5, BA 6	BA 4, BA 5, BA 6
	–54 –2 24**	3.6	30	BA 4, BA 6	
	–40 –8 –6**	3.3	107	Putamen	
	30 16 26**	3.2	40		BA 9
	20 –72 50*	2.8	35		BA 7
	30 –52 62*	2.7	31		BA 7
	34 4 16*	2.7	11		Posterior insula
Random warm stimuli #1	– 2 28 10**	4.9	1422	BA 6, BA 8, BA 24, BA 32 Caudate	BA 6, BA 8, BA 9, BA 10 BA 24, BA 32, caudate, putamen, globus pallidus
	–40 14 40**	4.5	355	BA 6, BA 9	
	–16 52 18**	4.2	261	BA 9, BA 10	
	4 –32 60**	4.0	77		BA 4, BA 5, BA 6
	–44 –26 4**	3.4	406	Posterior insula	
	44 –20 22**	3.0	74		Posterior insula
	–12 32 46*	3.0	127	BA8	
	30 –30 62*	3.4	11		BA 3
Pain: 47°C stimulus	40 –14 22**	4.5	2028		BA 3, BA 4, BA 6, anterior & posterior insula
	–4 4 4**	4.0	332	Caudate	Putamen, globus pallidus, caudate
	56 10 32**	4.0	141		BA 9
	–56 –42 34**	3.3	75	BA 40	
	44 –30 30**	3.2	46		BA 2, BA 40
	0 6 26**	3.1	70	BA 24, BA 32	BA 24, BA32
	24 –24 4**	3.1	33		Thalamus
	–4 30 28**	3.1	320	BA 6, BA 9, BA 32	BA 8, BA 32
	–40 –16 50*	2.8	20	BA 4	
Pain: temperature rated as 5	–40 16 8**	3.7	377	BA 9, anterior insula	
	–54 –30 16**	3.6	35	BA 40	
	–44 44 10**	3.1	24	BA 10	
	64 –28 18*	2.8	19		BA 40
	34 16 12*	2.7	10		Anterior insula
Random warm stimuli #2	–32 18 6**	4.3	646	BA 10, anterior insula	
	–4 8 52**	4.0	325	BA 6, BA 8, BA 24, BA 32	
	–10 –2 12**	3.7	188	Thalamus	Thalamus
	48 –58 36**	3.7	88		BA 40
	22 40 36**	3.6	177		BA 8, BA 9
	–14 48 32**	3.4	42	BA 9	
	–10 56 20**	3.3	24		BA 10
	12 2 60**	3.1	31		BA 6
	46 –36 18**	3.1	125		Posterior insula
	–30 16 40**	3.0	93	BA 8	
	12 12 –2**	2.9	19		Caudate, putamen
	0 –70 30**	2.9	78	BA 7	BA 7
	26 0 0*	2.5	5		Putamen

* $p \leq 0.005$, ** $p \leq 0.001$.

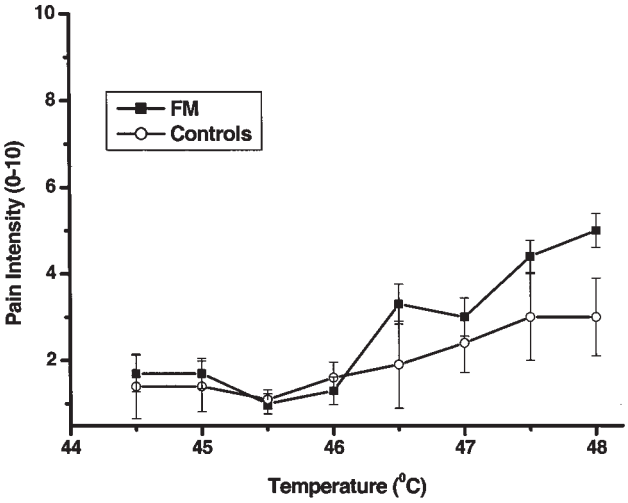

Figure 3. Mean pain intensity (± SE) for the 8 random heat stimuli in patients with FM (n = 9) and controls (n = 9).

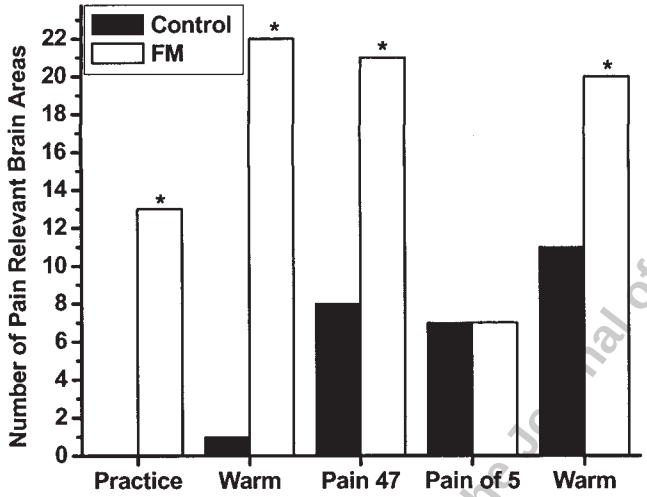

Figure 4. Number of significant a priori pain-related sites as a function of experimental condition for FM patients (n = 8) and healthy controls (n = 8). The figure shows the differences in pain-related brain regions across all experimental conditions. For each condition the areas of activation are based on within-subject's group analyses with significance set at $p < 0.01$. With the exception of the perceptually equivalent condition (pain rated as 5), FM subjects exhibited more pain-relevant brain areas in response to both nonpainful and painful heat stimuli (*p = 0.05, Fisher's exact test).

the control group. Further, as shown in Figure 5, neither the BOLD signals nor the design matrix was related to the measured movement variables.

Do FM patients exhibit pain-relevant activation to nonpainful warm stimuli? (Condition #2): perceptual ratings. There were no significant differences between groups for either the pain intensity or unpleasantness ratings for the 5 warm stimuli. Both groups generally rated the warm stimuli as not painful. The average pain rating for the warm stimuli was 0.5 (± 0.2) and 0.5 (± 0.3) for the FM and control groups, respectively. The average unpleasantness rating for the FM group was 1.3 (± 0.5) and for the control group 0.8 (± 0.4).

Within-group analyses. Warm stimulation resulted in significant activation in the contralateral dorsomedial nucleus of the thalamus in controls ($t = 3.7$, $p = 0.004$). The FM group exhibited bilateral activity in the prefrontal cortex (BA9, BA10), supplemental motor area (BA 6, BA 8), anterior cingulate cortex (BA 24, BA 32), the posterior insula, and the corpus striatum encompassing the caudate, putamen and a section of the globus pallidus. Contralateral activity was seen in the primary motor (BA 4) and sensory (BA 3) cortices.

Between-group analyses. The thalamic activation observed in the controls was not significantly different from the FM group. The FM group exhibited significantly greater activity bilaterally ($p < 0.01$) in the prefrontal [BA 9: (–22 26 40) (12 40 20), BA 10: (8 50 10)] and supplemental motor area {BA 8: (–8 32 46) (4 42 46)]. Significantly greater contralateral activity ($p < 0.01$) was observed in the anterior cingulate cortex [BA 32: (10 40 16)]. Controlling for depressed mood (BDI) and resting pain (MPQ) did not eliminate the differences, but only the contralateral areas remained significant (BA 9, BA 10, and BA 32).

Do FM patients exhibit greater neural responses to an absolute pain stimulus? (Condition #3 or #4): perceptual ratings. There were no significant differences between groups for either pain intensity or unpleasantness ratings. The average pain rating for the five 47°C stimuli was 2.2 ± 1.5 for the controls and 2.4 ± 2.1 for the FM group. Pain unpleasantness ratings for the 5 stimuli were 1.8 ± 1.8 for the controls and 2.7 ± 2.5 for the FM group.

Within-group analyses. Activation following five 47°C stimuli in FM patients and controls is illustrated in Figure 6. Areas of significant signal increase for the control group occurred predominantly in the contralateral hemisphere including the supplemental motor area (BA 6), sensory cortex (BA 2), and the cingulate cortex (BA 24). Bilateral activity was observed in the prefrontal cortex (BA 9), the putamen of the lenticular nucleus, and the medial dorsal nucleus of the thalamus.

The FM group exhibited robust activity mostly in the contralateral hemisphere (Figure 6); however, several areas showed bilateral activity. Bilateral activity was found in the primary motor cortex (BA 4), supplemental motor area (BA 6), prefrontal cortex (BA 9), inferior parietal cortex (BA 40), the anterior cingulate cortex (BA 24 and BA 32), and the caudate nucleus. Contralateral activation occurred in the sensory cortex (BA 2 and BA 3), the supplemental motor area (BA 8), the anterior and posterior insular cortex, the putamen and globus pallidus of the lentiform nucleus, and the thalamus including the ventroposterolateral nucleus and the pulvinar.

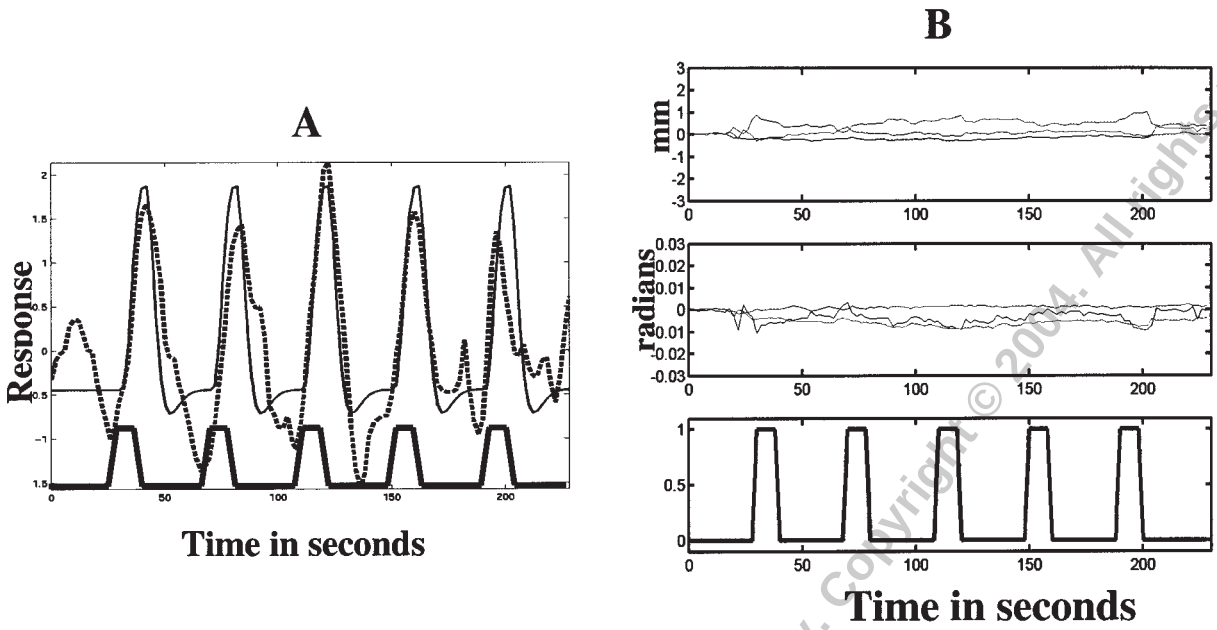

Figure 5. A. Relationship between the blood oxygen level-dependent (BOLD) activity and the experimental paradigm during practice in a representative patient with FM. The figure depicts the predicted hemodynamic adjusted response based on the experimental paradigm (solid lines), the actual response (broken line), and the superimposed block paradigm (bottom of the graph). (B) Movement parameters (x, y, z, roll, pitch, and yaw) for the practice session for the same patient. The figure depicts the movement of one subject in the x, y, and z directions (top panel) and the roll, pitch, and yaw directions (middle), as they related to the experimental block paradigm (bottom). Measured movement parameters were unrelated to either the experimental block paradigm or the BOLD response during the practice session.

Between-group analyses. None of the areas observed in the control group was found to be significantly greater than the FM group. For the FM group, significantly greater activity ($p < 0.01$) occurred in the contralateral insular cortex ([38 4–6]; Figure 7) compared to controls. Covariance for BDI or MPQ totals did not eliminate the difference.

Do FM patients exhibit greater neural responses to a perceptually equivalent pain stimulus? (Condition #3 or #4): perceptual ratings. The mean temperature rated as "5" for the control group was 48.3 ± 0.6°C. The average temperature for the FM group was 47.4 ± 1.4°C. The difference of almost 1° Celsius was large (Cohen d = 0.93). Moreover, the range of temperatures for the FM group was 45°C to 48°C, while the range for the control group was 47.5°C to 49°C. There were no significant differences between groups for self-reported pain intensity or unpleasantness ratings. The average pain rating for the 5 stimuli presented during fMRI scanning was 3.4 ± 1.3 for controls and 3.9 ± 2.6 for the FM group. Pain unpleasantness ratings were 2.8 ± 1.5 for controls and 3.2 ± 2.0 for the FM group.

Within-group analyses. Areas of significant activity for controls occurred bilaterally in the anterior insular cortex (Figure 8). Contralateral activity occurred in the supplemental motor area (BA 6), the prefrontal cortex (BA 9), and the inferior parietal cortex (BA 40). Ipsilateral activity was observed for the cingulate gyrus.

For the FM group, bilateral activity was observed in the inferior parietal (BA 40) and anterior insular cortices (Figure 8), although the insular activity was left lateralized (65 voxels on the left vs 6 voxels on the right). Ipsilateral activity was also observed in the prefrontal cortices (BA 9 and BA 10).

Between-group analyses. There were no significant differences in any brain areas for either FM or control group comparisons. Thus when a perceptually equivalent pain stimulus was delivered that consisted of greater absolute temperatures for the control group, there were no significant group differences in brain responses.

Do neural responses to nonpainful stimuli remain elevated following the presentation of several painful stimuli? (Condition #5): perceptual ratings. Consistent with Run #2, there were no significant differences in self-reported pain or unpleasantness for the 5 random stimuli. The average pain rating for the FM group was 0.4 (± 0.2) and for controls 0.04 (± 0.03). The average unpleasantness rating for the FM group was 0.8 (± 0.4) and for the control group 0.3 (± 0.1). The intensity ratings were a significant decrease from Run #2 for controls ($p < 0.05$), but not for the FM group.

Within-group analyses. The control group exhibited bilateral activity in the superior parietal cortex (BA 7) and the thalamus. Contralateral activity was also observed in the superior parietal cortex (BA 5), prefrontal (BA 10), anterior insular and cingulate (BA 23, BA 24, BA 31, BA 32) cortices. Although not an a priori region, the controls also

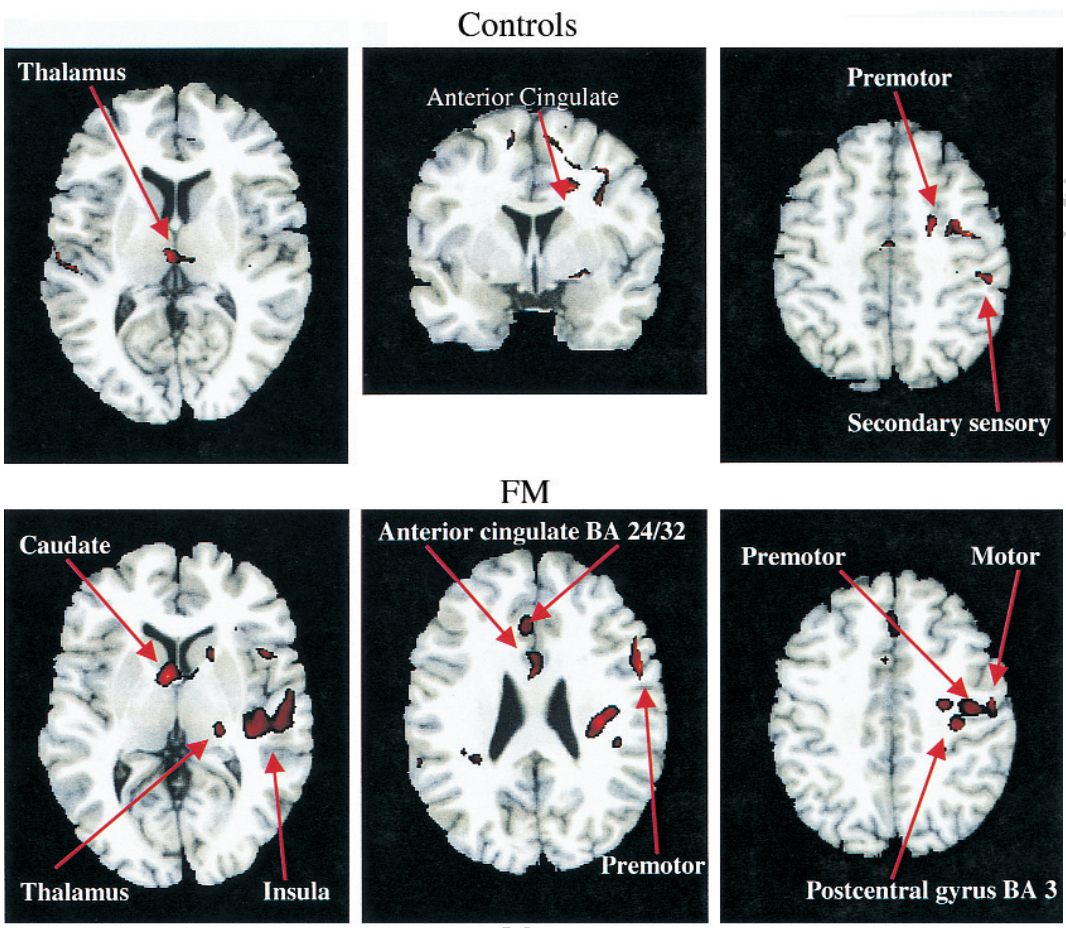

Figure 6. Pain-related activation in response to a 47°C stimulus in female controls (n = 8) and FM subjects (n = 8). Significant increases in fMRI signal are superimposed on a normalized T1 weighted brain and are based on a voxel-based whole-brain analysis of each group separately. FM patients exhibited a greater number of activated regions, and within similar regions a greater number of activated pixels.

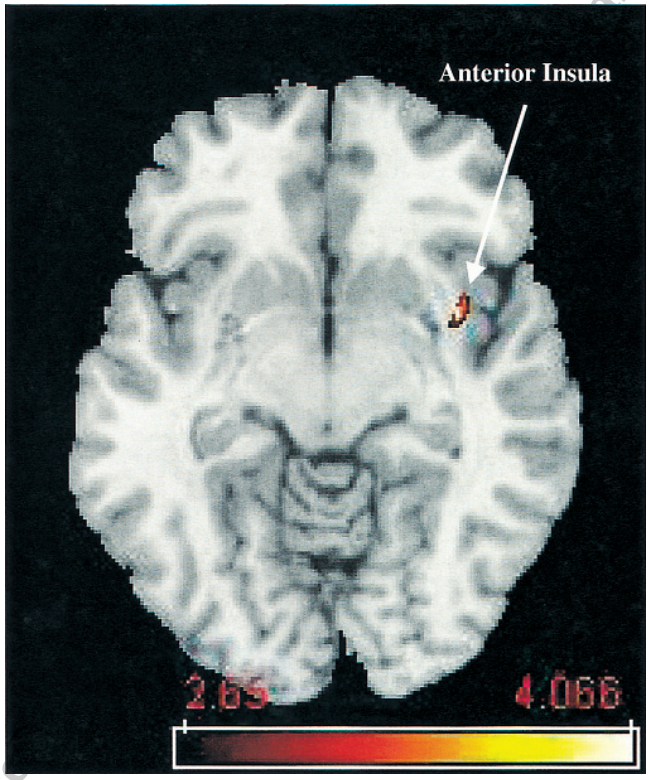

Figure 7. The greater BOLD signal in the anterior insular cortex of FM patients compared to controls. Significant increases in fMRI signal are superimposed on a normalized T1 weighted brain. Significance ($p < 0.01$) is based on a ROI analysis of a specific region of the anterior insula that exhibited significant activation in the within-group whole-brain search.

exhibited significant activity within the periaqueductal gray (PAG) of the midbrain (Figure 9).

The FM group exhibited bilateral activity in the supplemental motor areas (BA 6, BA 8), prefrontal (BA 9), superior parietal (BA 7), and anterior and posterior insular cortices. Bilateral activation was also observed in the ventral (left and right) and medial dorsal (left) nuclei of the thalamus. Contralateral activity was observed in the caudate and putamen. Ipsilateral activity was observed in the anterior cingulate cortex (BA 24 and BA 32).

Between-group analyses. Controls showed significantly greater activity ($p < 0.01$) in the contralateral medial dorsal

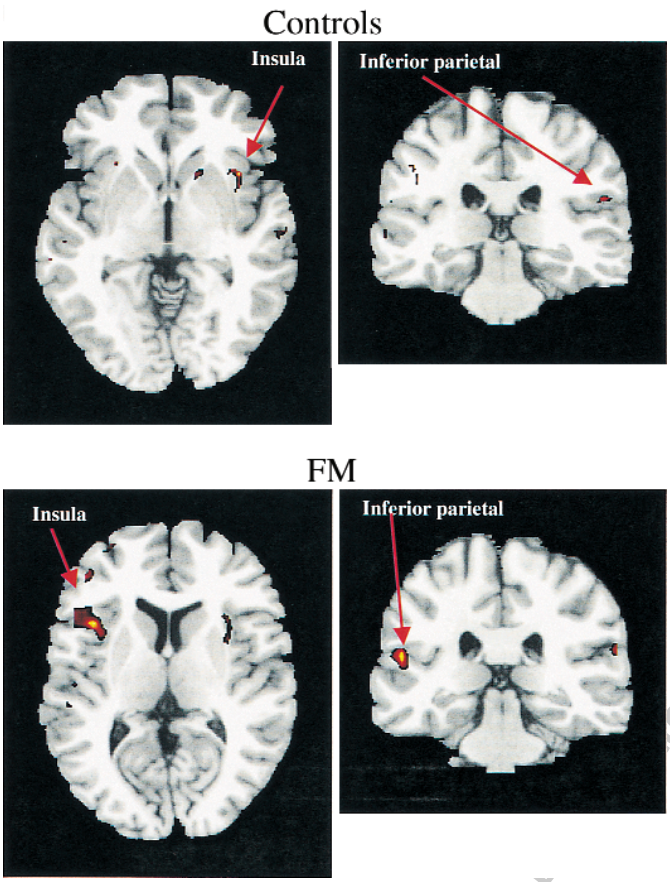

Figure 8. Pain-related activation in response to a perceptually equivalent pain stimulus (rated as 5) in controls (n = 8) and patients with FM (n = 8). Significant increases in fMRI signal are superimposed on a normalized T1 weighted brain and are based on a voxel-based whole-brain analysis of each group separately. When a perceptually equivalent stimulus was presented that was of an absolute lower stimulus in FM patients, qualitative differences in area and extent of activation were diminished.

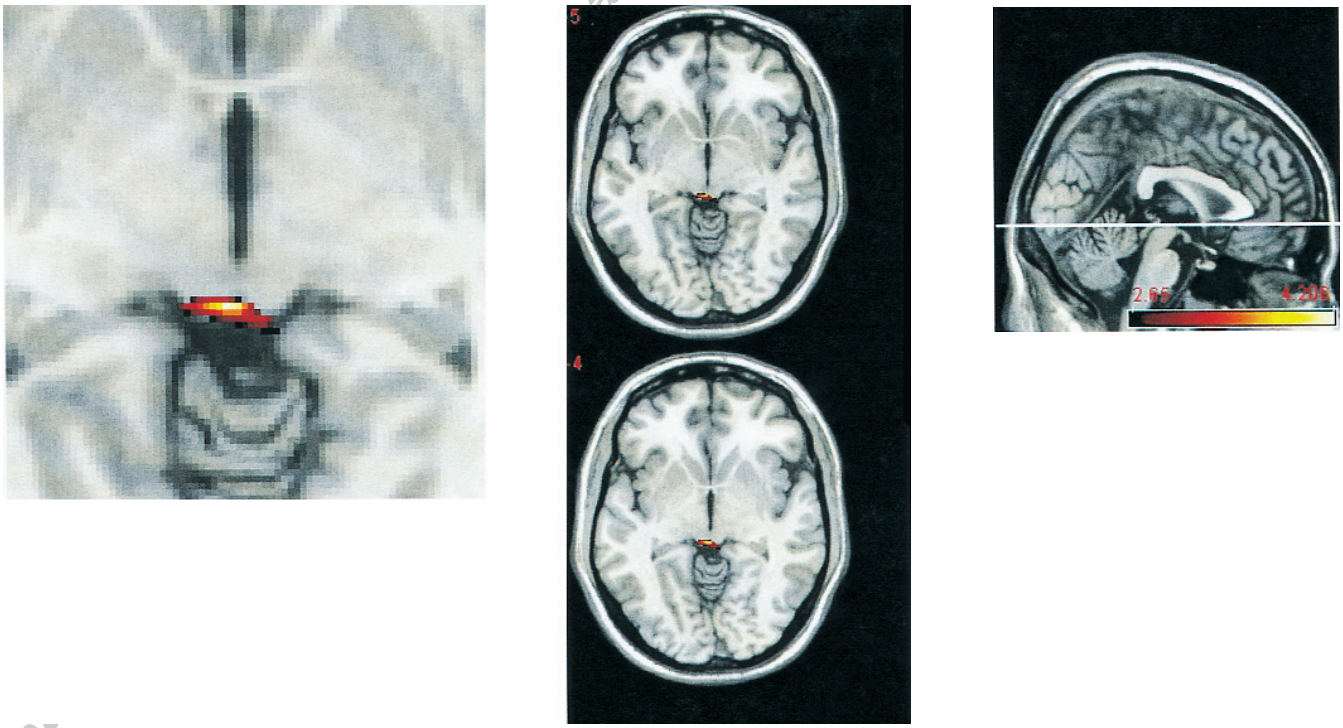

Figure 9. Periaqueductal gray (PAG) activation following several painful stimuli and in response to random warm stimuli in control subjects.

nucleus of the thalamus and the contralateral anterior cingulate cortex (BA 23: [5 –27 32] and BA 24: [5 –20 36]). ANCOVA with BDI total as the covariate resulted in only the contralateral anterior cingulate cortex (BA 23 and BA 24) activation remaining significantly greater than the FM group. Similar results were obtained with the MPQ total as the covariate. The FM group exhibited significantly greater activity ($p < 0.01$) in the ipsilateral insula [32 14 12]. ANCOVA for either BDI or MPQ did not change the results.

Relationship between subjective pain ratings and brain activity. Linear regression indicated that for both groups combined, self-reported pain intensity and unpleasantness were significantly ($p < 0.01$) related to bilateral activity in the cingulate cortex, contralateral activity in the sensory cortex (BA 2 and BA 3), and ipsilateral activity in the inferior parietal (BA 40) and anterior insular cortices.

DISCUSSION

Consistent with our hypotheses and previous research indicating dysregulation of the nociceptive system in FM[57-10,28], the FM group exhibited greater sensitivity to suprathreshold experimental pain stimuli and greater responses in multiple brain regions in response to both painful and nonpainful stimuli. For nonpainful warm stimuli, the greatest differences were observed in the prefrontal cortex, the supplemental motor area, the insula, and the anterior cingulate cortex. For painful heat stimuli, the greatest differences were observed in the anterior insular cortex. These results showing greater pain-related brain activity to both nonpainful and painful stimuli in patients with FM compared to controls provide support for a physiological explanation for FM pain, and suggest that FM symptoms may be maintained by amplified neural responses to afferent sensory stimuli. Our investigation was also designed to overcome several of the limitations of previous pain and brain imaging research and to apply some of the controls used in more recent brain imaging and pain studies[14,28,29]. In particular, and with the noted exceptions[14,28,29], brain imaging investigations of pain have not consistently controlled for attention, have not obtained concomitant pain ratings while delivering the pain stimulus, and have not measured pain in both absolute and relative terms. Therefore, we instructed subjects to focus on a set of pain scales during scanning and had them rate their pain intensity just prior to removal of the stimulus. This allowed us to examine more precisely the relationship between pain ratings and the BOLD response to the stimulus. We also examined pain in both perceptually equivalent and absolute stimulus terms to determine the importance of pain perception in FM and to make more meaningful group comparisons. Finally, we examined both painful and nonpainful stimuli to understand the function of the nociceptive system in FM. The fMRI results revealing similar psychophysical pain responses accompanied by greater neural responses in the FM group suggest that FM (not just pain sensitivity) is a disorder involving augmented physiological processing of nociceptive stimuli.

Perceptual and neural responses to nonpainful stimuli. The most striking feature of the results from the first set of warm stimuli was the host of pain-related areas activated in the FM group, but not the control group. Direct comparison between groups indicated that FM subjects had significantly greater activity in prefrontal, supplemental motor, and anterior cingulate cortices, compared to controls. These regions are well documented in pain and brain imaging research[44], and do not normally show significant activation when nonnoxious warm stimuli are delivered to healthy control subjects[13,15,16]. Greater activity in the prefrontal and anterior cingulate cortices suggests that cognitive and sensory aspects of pain such as anticipation, attention, and pain memories were greater in the FM group[44]. The role of the supplemental motor cortex in pain processing is less clear, but activity in this region may reflect motor inhibition to avoid withdrawal of the stimulated hand. Importantly, these differences were observed in the absence of any perceptual differences in pain or unpleasantness ratings, and were not eliminated when current depressed mood or pain was taken into account. Thus, the presence of BOLD responses to nonpainful stimuli occurring in regions of the brain normally associated with processing of painful stimuli provides evidence of augmented central responses to sensory stimuli in FM, and supports the contention that FM pain results from a dysregulation of the nociceptive system.

A second set of warm stimuli was given to determine the recovery of neural responses following the presentation of a series of painful stimuli. The results from the fMRI data suggest that neither group recovered completely. Both groups exhibited activity in pain-relevant regions. For the controls, this represented a very different response from that observed during the first set of warm stimuli, where only thalamic activity reached significance. For the FM group, the regions of activity were much the same as those observed during the previous warm and pain runs. Group comparisons indicated that the FM group had significantly greater activity in the ipsilateral insular cortex, a region consistently associated with pain perception[44]. Insular cortex activity dramatically increases as a stimulus changes from innocuous to noxious and is functionally implicated in sensory intensity coding[44]. Thus, greater activity in this area in the FM group indicates enhanced sensory coding of nonpainful heat stimuli and is supportive of augmented sensory processing. Moreover, the pattern of pain-relevant fMRI responses to both painful and nonpainful stimuli, and the significantly greater activity in brain areas involved in both cognitive (prefrontal and cingulate cortices) and sensory (supplemental motor, cingulate, and insular cortices) regions, is evidence that CNS dysregulation in the FM group was operating independent of stimulus condition.

The lack of thalamic activity in the FM group deserves mention, as this result is consistent with PET and SPECT studies in FM showing decreased thalamic blood flow[22,25]. Additionally, a recent fMRI study[28] described thalamic activation in response to pressure pain for controls but not patients with FM. This result was interpreted as tonic inhibition of thalamic nuclei in FM resulting from persistent excitatory afferent pain signaling. This theoretical mechanism is supported by results from other chronic pain conditions, where thalamic blood flow was normalized upon chronic pain relief[24,25]. Our results extend these findings by showing a similar result in response to a nonpainful stimulus. Another interesting observation during the final warm run was the presence of PAG activity in the control group but not the FM group. The PAG is well established as an important area involved in the descending modulation of nociceptive signals[45]. PET studies examining the cognitive and affective modulation of pain have reported PAG activity[46-49]. While not an a priori assumption, the absence of PAG activity in the FM group suggests that pain modulatory processes were not occurring after receiving several painful stimuli, while the pain regulatory system of the control subjects was actively attempting to inhibit further nociceptive input. These results are in agreement with investigations suggesting a dysregulation of noxious inhibitory controls in FM[5,7,8].

Perceptual and neural responses to painful stimuli. We gave both groups an absolute stimulus (47°C) and a relative stimulus (pain previously rated as 5) to examine whether differences observed between FM and control groups were due to the temperature delivered or to the perception of pain. To our surprise the FM group did not rate the 47°C stimulus as significantly more painful than the controls. Therefore, while Experiment 1 demonstrated that the FM subjects were generally more sensitive to experimental pain stimuli, this result did not generalize to the fMRI session. A review of the literature indicates that such a lack of differences is not unusual in FM. Petzke, *et al*[50] reported that FM patients found equal-pressure pain to be less unpleasant than a group of pain-free controls. Consistent with this result, our FM groups rated the 10 random pain stimuli delivered in Experiment 1 as more intense than controls but not more unpleasant. Moreover, investigations using similar psychophysical techniques have reported values consistent with those from our investigation[4,8].

In the absence of perceptual differences, the brain responses to the painful stimulus were quite different between the FM and control groups. When directly compared to the control group, the greatest difference occurred within the anterior insular cortex. The anterior insular cortex is the most consistent region of activation reported in pain and brain imaging studies[44]. That the anterior insula is implicated in intensity coding, and that activity within this region was greater in the FM group, is consistent with the view that FM pain is the result of augmented processing of nociceptive stimuli[28,44]. Specifically, the results showing similar pain ratings to the absolute stimulus but greater neural activity suggests that given the same afferent information, the physiological response of the FM patient is exaggerated. Additionally, qualitative differences were apparent both in the number of regions activated and in the number of pixels activated within a given region, further implicating augmented nociceptive processing. Thus, pain in FM may be due in part to an augmented central reaction to incoming sensory stimuli that remains elevated after the removal of the afferent signal. Evidence of an exaggerated wind-up response in FM that can be attenuated with an NMDA antagonist supports this contention and further suggests that NMDA receptor sensitivity may act to maintain CNS sensitivity in FM[9,51].

As intended, ratings for the relative stimulus were not different between the FM and control groups. However, for the FM group the temperatures necessary to reach a pain rating of 5 on the CR-10 scale were on average 1° Celsius lower than controls (48.3°C for controls and 47.4°C for the FM group). These temperatures represented a large change from the absolute 47°C stimulus for controls (1.3°C increase) and a small change for the FM group (0.4°C increase). Moreover, the range of pain temperatures indicated that patients and controls could differ by as much as 4°C, with a range of 45°C to 48°C in the FM group and a range of 47.5°C to 49°C in the control group. As a result, the controls showed an increase in activation that would be expected when a stronger painful heat stimulus is delivered[52], while the FM group exhibited fewer regions of activation, consistent with several subjects receiving an absolutely lower stimulus, and a general change in laterality from contralateral to ipsilateral dominance, the relevance of which is not presently clear. Thus, when a perceptually equivalent stimulus was delivered that was of an absolute greater intensity for the controls, the FM group exhibited a response similar to that of the control group. These results for painful heat are consistent with those of Gracely and colleagues[28], who demonstrated similar neural responses in FM patients and controls resulting from equal-pressure pain intensity. They interpreted their findings as evidence of central augmentation of pain in FM. Our results provide additional evidence of augmented pain processing in response to heat, and emphasize the need to compare perceptually relevant stimuli when examining FM pain.

Neural responses to the anticipation of pain. To account for potential brain activity associated with the movement required to rate the stimuli using the handheld device and the activity associated with the contact thermode touching the skin, we employed a practice session, when subjects practiced the rating task while not receiving any stimuli. This session allowed participants to become accustomed to the fMRI environment before receiving painful stimuli. As

expected, the controls did not show any activity above baseline in pain-relevant areas during this condition. This result is consistent with data reported by Davis, *et al*[19], using an event-related paradigm, showing no pain-related activation during a simulated ratings task. However, the FM group exhibited activity in several brain areas previously identified as pain-relevant that was not due to task-related movement. These areas included frontal, parietal, and insular cortices and suggest that the FM participants were anticipating a painful stimulus[53] or were in a heightened attentive state while rating, even after being informed that no stimulus would be delivered. Although we did not anticipate this finding, it raises the possibility that FM participants were more vigilant to the potential of incoming stimuli compared to controls. Hypervigilance to experimental pain stimuli in FM has been reported[4-6]. Research aimed at manipulating vigilance and examining fMRI responses is needed to determine what role vigilance plays in the neural representation of pain in FM.

Relationship between subjective pain ratings and brain activity. Pain ratings for both groups were significantly and positively related to increased activity in several pain-relevant brain regions. This result is encouraging, given that in many cases the self-report of pain does not correlate well with physiological indicators of pain (e.g., muscle damage). It is also in agreement with studies describing positive relationships between pain ratings and several brain regions, including those observed in our investigation[9,54]. Examination of a greater range of pain ratings may help to further delineate the role of specific brain regions involved in pain perception.

One potential limitation of this study is the small between-group differences observed in pain perception during fMRI testing. If we had observed greater differences in pain perception our results might have been different in magnitude but likely in the same direction as the current data. The absence of perceptual differences accompanied by an exaggerated neural response to the 47°C stimulus in FM actually strengthens the notion that FM pain, not sensitivity to an experimental stimulus, is a disorder of physiological processing of afferent sensory information. Another potential limitation is the modest between-group psychophysical differences observed in Experiment 1. While our results are similar to those of previous investigations, others have reported more robust psychophysical differences. Our choice of a reaction time-inclusive method for measuring pain threshold could be questioned. However, with a syndrome such as FM we would expect pain thresholds to be lower when using an ascending method of limits, since this approach capitalizes on the subject's anticipation of a painful stimulus. It is also important that our FM group may have comprised less severe cases than in previous investigations. For pilot study purposes, we screened our subjects to ensure they were free from clinical depression and not taking pain medications. This may have resulted in recruitment of a relatively high-functioning FM group, in which pain sensitivity was not inflated by comorbid depression. However, all subjects did meet stringent diagnostic criteria for FM[1]. Finally, the sample size of the study is a potential limitation. However, the robust differences in the fMRI experiment that remained even after controlling for potential confounds indicates that power was not a problem.

The etiology of FM is unknown, and no consistent underlying mechanism explaining FM pain has been identified. One theory that has emerged prominently in the literature focuses on the mounting evidence indicating abnormalities of the nociceptive system in patients with FM and attempts to explain FM pain as a dysregulation of the physiological processing of afferent sensory information. Our investigation was designed to test this theory by examining fMRI brain responses to both painful and nonpainful stimuli and examining pain in both absolute stimulus and perceptually-relevant terms. Consistent with our hypotheses, patients with FM exhibited neural activation in brain regions associated with pain perception in response to nonpainful stimuli, with the greatest differences occurring in prefrontal, supplemental motor, insular, and cingulate cortices. Also consistent with our hypotheses, patients with FM displayed greater activity than controls to an absolute pain stimulus but similar activity to a perceptually equivalent stimulus. The difference was most apparent in the anterior insular cortex, a region consistently associated with encoding of painful stimuli. Our results indicate that brain responses to sensory stimuli, in regions involved in sensory, cognitive, and emotional aspects of the pain experience, are augmented in FM. These results support a physiological explanation of FM pain and provide objective evidence of cortical and subcortical amplification of both painful and nonpainful thermal stimuli.

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APPENDIX

Pain Threshold Methods for Experiment 1

Prior to threshold measurement, participants were given a standard set of instructions for both heat and pain threshold assessments. For heat threshold, participants were asked to indicate, by pressing a mouse button with their free hand, the point at which they felt any change in temperature. For pain threshold, participants were asked to indicate when the warm sensation became "just painful" and were reminded that this was not a test to see how much pain they could tolerate. Three sets of heat stimuli followed by 3 sets of pain stimuli were delivered separated by 3 minutes each. Each set consisted of 3 threshold measurements. Heat and pain thresholds were defined as the average temperature of sets 2 and 3.

Suprathreshold Pain Methods for Experiment 1

During testing, the subject could see the pain scales using a set of fiber optic goggles (Avotec, Jensen Beach, FL, USA). The goggles were interfaced with a laptop computer (Gateway 2000) for display. To obtain ratings during the painful stimulus without the subject's verbal response, ratings were made using a keypad. The keypad was placed in the participant's right hand for recording pain scores and a Labview program (National Instruments, Austin, TX, USA) allowed the subject to scroll up or down the pain scale until the appropriate number representing their pain perception was selected. Following a standard set of instructions describing the purpose and use of the pain intensity and unpleasantness scales, the subject reclined on an examination table and the Peltier thermode was attached to the hand. Subjects were told that they were about to receive a number of stimuli, some of which may be "extremely painful," but that no skin damage would result. Subjects were prompted to record their ratings during the last 5 s of each 10 s stimulus period.

Experimental Paradigm for fMRI Testing

Run 1 (Condition 1) was used to examine the potential activation associated with the thermode touching the skin (no stimulus given) and the small movement required for rating with the right hand. Participants were told that no stimulus would be delivered and were given a number to record during the last 5 s of each on-period. Runs 2 and 5 (Conditions 2 and 5) consisted of 5 random warm stimuli ranging from 34°C to 42°C in 2°C increments. Participants all received the same random sequence and were prompted during the last 5 s of each stimulus to rate the pain intensity. Runs 3 and 4 consisted of painful heat stimuli. One run consisted of five 47°C stimuli and the other consisted of a temperature that was previously rated as a 5 ("strong pain") on the 0–10 pain intensity scale in Experiment 1. The runs were counterbalanced so that half the subjects received the absolute stimulus (47°C) first and half received the relative stimulus (temperature previously rated as 5; the verbal anchor "strong pain") first. The separate presentation of absolute (47°C) and relative (temperature previously rated 5) stimuli was intended to examine if fMRI brain responses to painful heat are different when the stimuli are: (a) objectively identical but perceptually distinct (absolute 47°C stimulus) versus (b) perceptually identical but objectively distinct (stimulus previously rated as 5, "strong pain"). Immediately after each run, participants rated their peak pain unpleasantness (0–10).