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Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia

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Objective. **To use functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during the application of painful pressure and determine whether this pattern is augmented in patients with fibromyalgia (FM) compared with controls.**

Methods. **Pressure was applied to the left thumbnail beds of 16 right-handed patients with FM and 16 right-handed matched controls. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with those in controls, who were tested under 2 conditions: the "stimulus pressure control" condition, during which they received an amount of pressure similar to that delivered to patients, and the "subjective pain control" condition, during which the intensity of stimulation was increased to deliver a subjective level of pain similar to that experienced by patients.**

Results. **Stimulation with adequate pressure to cause similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in patients. Increased fMRI signal occurred in 7 regions common to both groups, and decreased signal was observed in 1 common region. In contrast, stimulation of controls with the same amount of pressure that caused pain in patients resulted in only 2 regions of increased signal, neither of which coincided with a region of activation in patients. Statistical comparison of the patient and control groups receiving similar stimulus pressures revealed 13 regions of greater activation in the patient group. In contrast, similar stimulus pressures produced only 1 region of greater activation in the control group.**

Conclusion. **The fact that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or subcortical augmentation of pain processing.**

Fibromyalgia (FM) is characterized by chronic widespread pain (involving all 4 quadrants of the body as well as the axial skeleton) and diffuse tenderness (1). Population-based studies have demonstrated that FM affects ~2–4% of the population, with a very similar prevalence in at least 5 industrialized countries (2,3). The etiology of FM remains elusive, although there is support for the notion that altered central pain processing is a factor in the presentation of this disease. The development of functional brain imaging techniques provides an opportunity to examine central pain processing in patients with FM.

Although the clinical diagnosis of FM is based on detecting 11 of 18 tender points (regions that are painful when manually palpated with 4 kg of pressure), increased sensitivity to pressure in this condition extends beyond tender points and involves the entire body (4–7). In aggregate, psychophysical studies demonstrate that patients with FM and control subjects generally *detect* sensory stimulation (electrical, thermal, mechanical) at the same levels, but the level at which these stimuli become unpleasant or noxious (pain threshold) is lower in patients (8–11).

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The subjective nature of FM symptoms has led to a longstanding debate regarding the legitimacy of this condition (12,13) and the predominant mechanism(s) involved in FM (14–16). A generalized increase in pain sensitivity could be attributable to psychological (e.g., hypervigilance, expectancy) or physiologic (e.g., central sensitization or other subcortical amplification processes) mechanisms. In a clinical setting, the focus is frequently on the difficulty in managing these patients and the veracity of their complaints (17,18).

Functional neuroimaging is a valuable tool for the analysis of mechanisms involved in human pain processing. A variety of functional imaging techniques consistently reveal a group of brain structures that are activated during painful conditions. Positron emission tomography (PET) and, recently, functional magnetic resonance imaging (fMRI) show that painful thermal, electrical, chemical, and pressure stimulation result in increased regional cerebral blood flow (rCBF) in structures involved in the processing of sensation, movement, cognition, and emotion (19–21). Pain stimulation–related neural activity is inferred from this increase in rCBF, because focal increases in activity are known to trigger a spatially and temporally localized increase in flow to meet increased neural metabolic demands.

Functional neuroimaging has only recently been applied to the evaluation of conditions such as FM. In a study by Mountz et al, single-photon–emission computed tomography (SPECT), which evaluates rCBF over a period of 30 minutes, revealed diminished resting rCBF in bilateral thalami and caudate nuclei in 10 patients with FM compared with 7 control subjects (22). A recent study by Kwiatek et al, using 17 FM patients and 22 controls, replicated the reduced rCBF in the right thalamus and demonstrated a trend toward reduced rCBF in the left thalamus (23). That study also showed reduced rCBF in the inferior dorsal pons and in a restricted region of the right lentiform nucleus.

SPECT designs provide static baseline measures of rCBF in patients at rest. As noted by Pillemer et al, measurement problems in patients with FM may be decreased and experimental power increased by dynamic designs that include the evaluation of physiologic responses during baseline and stimulation conditions (24). SPECT can be applied to assess the response to an intervention such as a painful stimulation by repeating the 30-minute evaluation following the intervention. Dynamic effects during shorter time periods can be assessed by increasing the 30-minute temporal resolution to 1 minute using PET methodology and to less than 5 seconds using fMRI. Because of this and other features of fMRI, such as increased spatial resolution and lack of radioactive tracers, this method has rapidly been applied to the investigation of a wide range of clinical conditions.

In the current study, the spatial and temporal resolution of fMRI brain imaging were used to characterize the pattern of increased rCBF produced when blunt pressure was applied to the thumbnail beds of 16 patients with clinical tenderness associated with the diagnosis of FM. These patterns of response were compared with those evoked in 16 control subjects. The experimental design addressed the simple question, "Does the pattern of brain activation in FM patients match that produced by equally low stimulus pressures in normal volunteers, or does it match that produced by equally subjectively painful stimuli (produced by significantly greater stimulus pressures) in the normal volunteer group?" A match of equal subjective pain intensities is consistent with a pathologic increase in pain sensitivity in patients.

PATIENTS AND METHODS

Patients and control subjects. Sixteen non–clinically depressed right-handed patients (15 women, 1 man; mean ± SD age 52.6 ± 12.3 years, range 19–69) who met the 1990 American College of Rheumatology criteria for FM (1) at the time of the study were randomly recruited from a sample of 165 consecutive clinic patients. Patients were allowed to continue taking any long-term medications, although analgesics were discontinued 12 hours before the baseline psychophysical evaluation and the fMRI sessions. Patients receiving opioid medications were excluded. Sixteen healthy control subjects (15 women, 1 man; age 45.8 ± 10.5 years, range 22–61) were recruited through newspaper advertisements and were compensated for their participation. All subjects provided a history and underwent a physical examination to screen for concurrent illnesses, including depression (using the Beck Depression Inventory), and the menstrual phase of all female participants was determined. All subjects gave informed consent before testing. The protocol was approved by the Georgetown University Institutional Review Board.

Psychophysical assessment. In a pre-fMRI baseline session, pressure pain sensitivity was evaluated by subjective scaling of suprathreshold sensations using a combined numerical analog descriptor scale of pain intensity and unpleasantness (25). Discrete pressure stimuli of 5 seconds in duration were applied to the left thumbnail with a 1-cm^2 hard rubber probe attached to a hydraulic piston. A combination of valves and calibrated weights produced controlled, repeatable stimulation that approached a rectangular waveform. Subjects rated the intensity and unpleasantness of pressure pain sensations evoked by an ascending series of stimuli, beginning at 0.45 kg/cm^2 and ascending in 0.45/cm^2-kg steps up to tolerance or to a maximum of 9 kg/cm^2. Following the ascending series, 7 stimuli (intensities of 0.45, 0.9, 1.35, 1.8, 2.7, 3.6, and 4.5

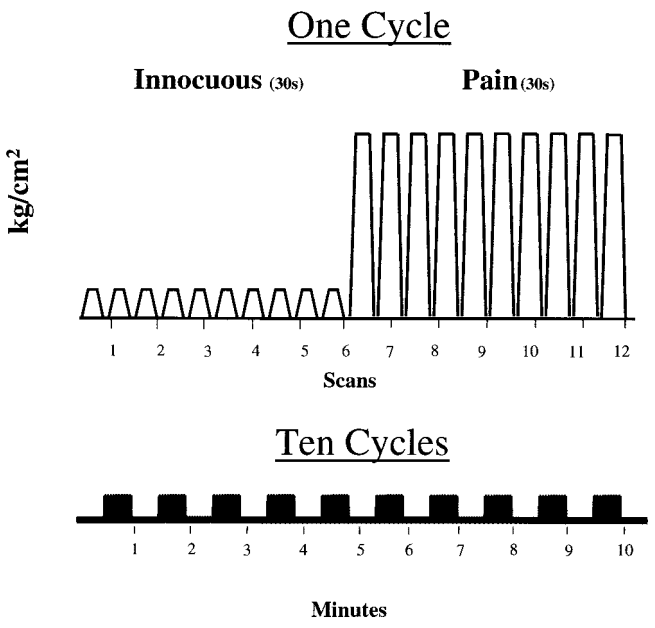

Figure 1. Sequence of events during a single scan. During 1 cycle, stimulus pressure is increased to a level that evokes innocuous tactile sensations and applied for 30 seconds, then is increased to a painful level and applied for 30 seconds. Both types of stimuli are decreased for 0.3 second at 3-second intervals. Functional images of the entire brain are obtained at 5-second intervals, resulting in 6 functional volumes for each 30-second stimulus. A cycle is repeated 10 times, for a total of 120 volumes collected over 10 minutes. Three additional scans performed at the beginning of the series are not analyzed to allow for equilibration of the functional magnetic resonance imaging signal, and 5 scans at the end of the sequence are not analyzed.

kg/cm^2) were delivered twice in random order. The interstimulus interval was 20 seconds.

Psychophysical analysis. For each subject, pressure pain thresholds during the ascending series were defined as the mean of the highest stimulus intensity that received all responses of zero and the lowest stimulus intensity that received at least 1 response indicating pain. The psychophysical function describing pain magnitude versus stimulus intensity was used to estimate stimulus intensities that would evoke a pain intensity of 11 ("moderate") in patients and healthy controls. This method was also used to determine a stimulus intensity that would evoke a mean pain intensity of 3 ("faint" to "very weak") in control subjects. The response value of 3 in controls was chosen from preliminary data, because the stimulus intensity needed to produce this subjective level closely matched the intensities needed to evoke a response of 11 in patients. These intensities were used in a simulation procedure 2–24 hours before the actual scan. Pain intensity was recorded every 10 seconds over complete 10-minute runs following the same 30-second on-and-off cycles used in the scanner to ensure that subjects were able to tolerate the pressure stimulation and that the evoked sensations were in the desired subjective range.

Functional imaging. MRI and fMRI scans were performed on a 1.5 Tesla vision system (Siemens, Munich, Germany). T1-weighted MRI anatomic scans (time to echo [TE] 4 msec; time to recovery [TR] 9.7 msec; flip angle 12°; 256 × 256–pixel matrix; field of vision [FOV] 256 mm; 1-mm^3 voxels, acquired noninterleaved in the sagittal direction) were followed by 1 or 2 functional scans using multislice echo-planar imaging fMRI acquisition (TE 40 msec; TR 5 seconds; repetition time 5 seconds; flip angle 90°; 64 × 64–pixel matrix; FOV 192 mm; 50 horizontal 3-mm slices). These parameters allowed coverage of the entire brain with 3-mm^3 voxels.

A sequence of 128 time points (brain volumes) per run was obtained (1 stimulation condition per run). The results from 8 time points (3 in the beginning, 5 at the end) were discarded, leaving 120 scans for the analysis. In each stimulation condition, subjects alternately received 30 seconds of innocuous touch and 30 seconds of painful pressure, for a total of ten 1-minute cycles. Onset and offset were coincident with the beginning of a scan, and the series was initiated on the third scan. At 3-second intervals, stimulating pressure was decreased for 0.3 second to avoid occlusion of blood flow. These parameters are represented in Figure 1, which shows the time course of a single stimulus cycle and that of a complete scan.

Imaging analysis. Imaging data were analyzed with MEDx (Sensor Systems, Sterling, VA). The functional images were corrected for head motion and intensity differences. Excessive head motion was determined by motion detection software and visual inspection of raw and processed images. Acceptable motion-corrected images were spatially smoothed at 6-mm full width at half maximum. The 60 volumes collected during the touch condition and the 60 volumes collected during the pain conditions were compared by *t*-test. Resultant Z statistical maps were registered into standardized space using the statistical parametric mapping (SPM96) echo-planar imaging template and resliced to 2-mm^3 voxels.

Group Z maps were computed from the sum of individual Z maps divided by the square root of N. Activations were considered significant at $P < 0.05$, corrected for multiple comparisons using the random Gaussian field theory correction (26). This correction recognizes the correlation between neighboring voxels due to spatial smoothing and reduces the number of elements used to calculate the correction to the actual number of independent elements. A directed search evaluated activations in a priori regions that were determined in a previous study of pressure pain sensitivity using 54 scans obtained from 27 control subjects (ref. 27 and Gracely RH, et al: unpublished observations). A post hoc analysis searched for activations in the entire brain, including white matter and regions of gray matter not previously implicated in pain processing.

For comparisons of conditions between FM patients and controls, clusters within a condition were defined as a volume of activations with at least 1 statistically significant voxel (corrected $P < 0.05$) and adjacent surrounding voxels with an uncorrected significance of $P < 0.005$ or greater. Significant differences between conditions were assessed by *t*-test, and the significance level was corrected for multiple comparisons using the random Gaussian field theory correction (26). A directed search examined all voxels showing significant activation in any condition, and an additional

Table 1. Significant increases in signal for the subjective pain control condition (high pressure, high pain)*

Side	Region	Coordinate			Z score
		x	y	z	
Sensory cortex					
Contralateral	Primary somatosensory cortex	54	−20	44	4.25†
Ipsilateral	Primary somatosensory cortex	−52	−22	52	−4.58†
Contralateral	Secondary somatosensory cortex	64	−26	22	4.04†
Contralateral	Inferior parietal lobule	54	−30	26	3.66
		52	−52	48	4.06
		48	−54	38	5.00†
Contralateral	Insula	38	4	0	3.79†
Ipsilateral	Insula	−48	12	−2	4.28
Frontal cortex					
Contralateral	Inferior frontal gyrus	54	16	2	4.07
Motor cortex					
Contralateral	Supplementary motor area	12	2	68	4.51
Contralateral	Supplementary motor area	2	2	58	5.35
Ipsilateral	*Precentral gyrus*	*−46*	*2*	*8*	*3.72*
Subcortical motor					
Contralateral	Caudate nucleus	14	4	20	4.32
Contralateral	Putamen	28	6	−2	5.51†
Ipsilateral	Globus pallidus	−12	0	2	4.90
Thalamus					
Contralateral	Ventral anterior nucleus	12	−8	12	4.71
Contralateral	Anterior nucleus	6	−4	6	5.04
Contralateral	Ventral lateral nucleus	12	−14	2	4.90
Ipsilateral	Ventral lateral nucleus	−12	−12	6	6.03
Temporal cortex					
Contralateral	Superior temporal gyrus BA22	60	12	−6	5.23†
Ipsilateral	*Superior temporal gyrus BA22*	*54*	*10*	*−4*	*3.89*
Cerebellum					
Ipsilateral	Anterior lobe	−24	−48	−30	6.61†
		−36	−44	−38	5.75
Ipsilateral	Posterior lobe	−50	−58	−36	4.56
Contralateral	Posterior lobe	28	−70	−32	6.34

* Italics indicate the stimulus pressure control condition (low pressure, low pain). IPL = inferior parietal lobe.
† Matches activations in the patient condition.

general analysis included the entire brain. Anatomic regions were identified by inspection of individual functional images superimposed on an individual structural image and by conversion of the coordinates to the coordinate system of the Talairach-Tournoux atlas and localization using this atlas (28) and automated software (29).

RESULTS

FM patients displayed significantly lower pressure pain thresholds at the left thumbnail compared with those displayed by control subjects, as determined by either a clinical method of ascending series (mean ± SEM 1.4 ± 0.28 versus 2.7 ± 0.23 kg/cm^2; t [30] = 3.62, $P < 0.001$) or extrapolated from the suprathreshold ratings (mean ± SEM 0.8 ± 0.08 versus 1.1 ± 0.03 kg/cm^2; t [30] = 4.06, $P < 0.0001$). In 3 control subjects, the imaging results in both conditions could not be interpreted because of excessive head motion; the data for these 3 subjects were excluded from further analysis. A fourth control subject showed unacceptable head motion in the low-pain condition, and these imaging data were excluded; however, the imaging data from the high-pain condition and the psychophysical data for this subject were included in the analysis. After subject exclusion, differences in thresholds were still highly significant for the ascending series (mean ± SEM 1.4 ± 0.28 versus 2.7 ± 0.28 kg/cm^2; t [27] = 3.33, $P < 0.005$) and for the extrapolated suprathreshold method (mean ± SEM 0.8 ± 0.08 versus 1.1 ± 0.03 kg/cm^2; t [27] =3.63, $P < 0.001$).

Analysis of the self reports about menstrual phase, which were obtained at the time of screening and on the day of the scan, classified the female subjects as premenstrual, menstrual, follicular, midcycle, luteal, or postmenopausal. The frequencies of these categories were 0, 5, 2, 0, 0, and 6, respectively, among control subjects and 0, 1, 3, 1, 1, and 9, respectively, among

Table 2. Significant increases in signal for the patient condition (low pressure, high pain)

Side	Region	Coordinate			Z score
		x	y	z	
Sensory cortex					
Contralateral	Primary somatosensory cortex	52	−16	44	4.58*
Ipsilateral	Primary somatosensory cortex	−48	−24	52	−4.16*
Contralateral	Secondary somatosensory cortex	52	−20	16	5.22
Ipsilateral	Secondary somatosensory cortex	−58	−24	14	5.40
Contralateral	Inferior parietal lobule	54	−20	30	4.22
		64	−32	24	4.14*
Contralateral	Inferior parietal lobule BA40	58	−38	36	4.10*
Contralateral	Insula	36	6	6	3.70*
Subcortical					
Contralateral	Putamen	26	2	4	3.64*
Temporal cortex					
Contralateral	Superior temporal gyrus	62	10	2	4.68*
Ipsilateral	Superior temporal gyrus	−70	−28	16	3.68
Cerebellum					
Ipsilateral	Posterior lobe	−28	−60	−30	4.30
Ipsilateral	Anterior lobe	−20	−54	−32	4.21*

* Matches activations in the subjective pain control condition.

patients. Self reports for 2 control subjects were missing. These data were analyzed by chi-square tests that included the 2 subjects with missing data in "worst-case" categories, which would make the greatest contribution to a significant difference in frequencies between the 2 groups. Analysis of neither the entire data set ($X[5] = 5.7$) nor of reduction to nonmenopausal cases ($X[4] = 4.85$) or to 2×2 tables of premenopausal versus postmenopausal ($X[1] = 0.533$, Yates' correction) resulted in a significant difference between groups.

Figure 2 shows the relationship between conditions, stimulus intensities, and pain magnitudes. Patients received a single functional scan with a mean stimulus intensity of 2.4 kg/cm^2, which was sufficient to evoke pain sensations (mean ± SD rating 11.30 ± 0.90). Healthy controls received a similar functional scan, but a greater mean stimulus intensity (4.16 kg/cm^2) was needed to evoke pain sensations of the same magnitude (mean ± SD rating 11.95 ± 0.94) as those experienced by FM patients. Controls also received a second functional scan with stimulus intensities (2.33 kg/cm^2) similar to those administered to patients, which produced less-intense pain sensations (mean ± SD rating 3.05 ± 0.85).

Tables 1 and 2 show the anatomic location, standard coordinates, and statistical Z value for the peak voxel activations. The low stimulus pressures delivered to patients resulted in 12 significant regions of increased rCBF. In contrast, these relatively low stimulus pressures resulted in only 2 significant activations in the control group. Increasing the pressures applied to controls to a level sufficient to evoke levels of pain similar to those experienced by patients produced 19 significant regions of increased rCBF in healthy control subjects.

Tables 1 and 2 and the color images in Figure 2 show overlapping and adjacent areas of activation. Delivery of high levels of subjective pain in both controls and patients resulted in 7 common regions of increased fMRI signal. These focal regions of putative increased neural activity were located in the contralateral (right) primary somatosensory cortex, secondary somatosensory cortex, inferior parietal lobule cortex, superior temporal gyrus, insula, and putamen, and the ipsilateral cerebellum. Use of high subjective pain conditions also resulted in a single common region of decreased signal in the ipsilateral primary somatosensory cortex.

In contrast to the results obtained with equivalent pain intensities, applying the low levels of pressure used in the patient group to healthy controls resulted in significant increases in fMRI signal in the contralateral superior temporal gyrus at the temporal pole and in the ipsilateral premotor cortex. Neither of these activations overlapped with significant increases in fMRI signal evoked by similar levels of stimulus pressure in the patient group.

High subjective pain in the control group also produced increased rCBF in regions that were not observed in the patient group. Table 1 and Figure 2 show activation in several regions involved in motor function, including the contralateral supplementary motor area, contralateral caudate nucleus, and ipsilateral globus pallidus. The prominent bilateral activations in ventral lateral thalamic nuclei and the activation in contralateral

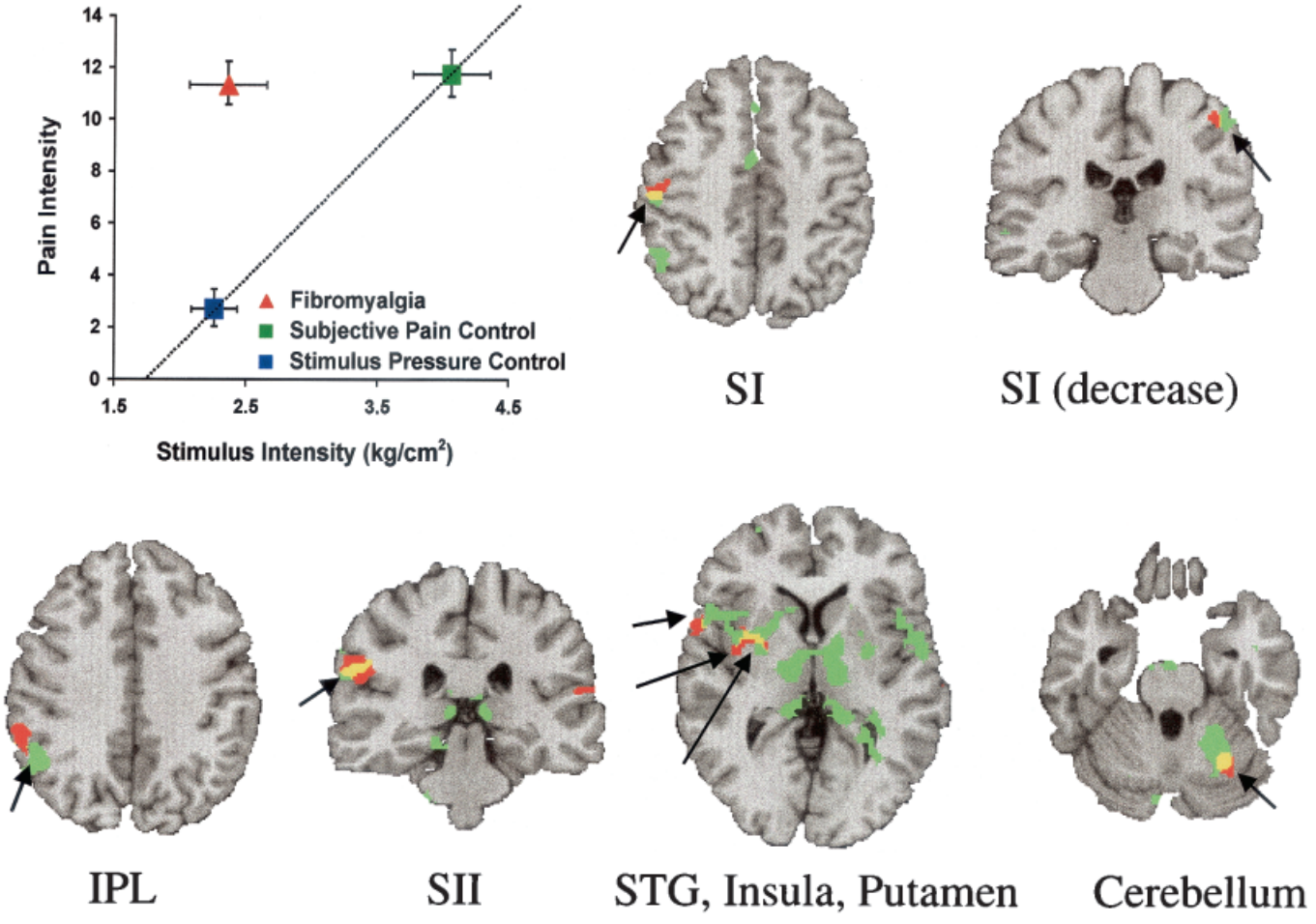

Figure 2. Stimuli and responses during pain scans. Common regions of activation in patients (red) and in the subjective pain control condition (green), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) are compared with the effects of innocuous pressure. Significant increases in the functional magnetic resonance imaging (fMRI) signal (**arrows**) resulting from increases in regional cerebral blood flow (rCBF) are shown in standard space superimposed on an anatomic image of a standard brain. Images are shown in radiologic view, with the right brain shown on the left. Overlapping activations are shown in yellow. The similar pain intensities, produced by significantly less pressure in patients, resulted in overlapping or adjacent activations in the contralateral primary somatosensory cortex (SI); inferior parietal lobule (IPL); secondary somatosensory cortex (SII); superior temporal gyrus (STG), insula, and putamen; and in the ipsilateral cerebellum. The fMRI signal was significantly decreased in a common region in the ipsilateral SI. Compared with stimulation with innocuous pressure, stimulation of healthy controls by the pressure levels used in the patients evoked significantly less pain and 2 regions of significant increases in rCBF, in the ipsilateral superior temporal gyrus and precentral gyrus (not shown). Neither of these regions coincided with regions of activation in the patient group. The graph shows mean pain rating plotted against stimulus intensity for the experimental conditions. In the fibromyalgia condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (mean ± SD 11.30 ± 0.90). In the stimulus pressure control condition, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (mean ± SD 3.05 ± 0.85). In the subjective pain control condition, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain (mean ± SD 11.95 ± 0.94) similar to those produced in patients by lower stimulus pressures.

ventral anterior nucleus are also localized to regions that subserve a motor function. An additional activation is localized to the contralateral anterior nucleus, an integral part of the limbic system.

Tables 1 and 2 and Figure 2 show that the effects in the patient and control groups were similar when the subjective pain control condition was applied to controls, which supports the hypothesis of augmented pain sensitivity in FM. Table 3 and Figure 3 show the results of direct comparisons between the patient group and the equal stimulus pressure control condition, which directly tests this hypothesis. Data from the 2 groups were compared by

Table 3. Comparison of patient condition (low pressure, high pain) and equal stimulus pressure control condition (low pressure, low pain)

Side	Region	Coordinate			Z score
		x	y	z	
Frontal cortex					
Ipsilateral	Medial frontal gyrus	−10	64	16	−3.02
Sensory cortex					
Contralateral	Primary somatosensory cortex	55	−18	29	3.15
Contralateral	Inferior parietal lobule	52	−40	38	3.43
		58	−28	28	3.02
Contralateral	Insular cortex	36	4	6	3.09
Ipsilateral	Secondary somatosensory cortex	−58	−24	14	3.93
Temporal cortex					
Contralateral	Superior temporal gyrus	46	−54	10	3.56
		64	−52	18	3.03
Ipsilateral	Superior temporal gyrus	−54	−2	0	3.19
Limbic cortex					
Contralateral	Anterior cingulate cortex	1	8	30	3.25
Contralateral	Posterior cingulate cortex	12	−56	6	3.05
		4	−46	40	3.05
Motor regions					
Contralateral	Cerebellum	18	−60	−32	3.31
Ipsilateral	Cerebellum	−30	−62	−26	3.86

first reducing the results of each scan in each person from a 3-dimensional (3-D) statistical volume to a 3-D volume of mean difference in signal between the on and off conditions for each scan. These mean difference volumes between the patient condition and the stimulus pressure control condition were compared on a voxel-by-voxel basis by unpaired *t*-tests. This statistical comparison can be classified as a mixed model that allows generalization of results in the subject sample to the population of control subjects and FM patients. These tests are also relatively conservative, ignoring the statistical information inherent in each scan, and attenuated by imperfect normalization to a standard brain shape.

Table 3 and Figure 3 show that the effects of the similar stimulus pressures resulted in 13 regions in which the fMRI signal was significantly greater in patients than in controls. These regions include the contralateral primary somatosensory cortex, inferior parietal lobule, insular cortex, anterior and posterior cingulate, ipsilateral secondary somatosensory cortex, and bilateral superior temporal gyrus and cerebellum. In contrast, these stimulus pressures resulted in only 1 region in which the signal was significantly greater in controls. This region was located in the ipsilateral medial frontal gyrus (Figure 3); it is presented in Table 3 as a negative Z score.

DISCUSSION

In FM patients, application of mild pressure produced subjective pain reports and cerebral responses that were qualitatively and quantitatively similar to many of the effects produced by application of at least twice the pressure in control subjects. Activations were observed in the contralateral primary and secondary sensory cortices, consistent with findings using brief or tonic thermal stimuli and tonic mechanical stimulation (30–32). These activations were more pronounced in patients, and the activation in the secondary somatosensory cortex in patients was also observed on the ipsilateral side, suggesting an augmentation of painful input to structures involved in processing the sensory discriminative components of pain. Stimulation sufficient to produce equivalent levels of pain in patients and controls also produced prominent and similar activations in the ipsilateral cerebellum (Figure 3). Other regions with significant activations in both groups included contralateral putamen, inferior parietal lobule, and superior temporal gyrus. Both groups also showed a common significant decrease in signal in the ipsilateral primary somatosensory cortex. The finding of similar activations despite lower amounts of stimulation has also been observed in patients with allodynia caused by cerebral infarction (33).

The overlap between activations in patients and activations evoked with greater stimulus pressures in control subjects provides one line of evidence consistent with augmentation of pain sensitivity in patients with FM. A second line of evidence is provided by the comparison of the similar stimulus intensity conditions. Application of mild pressure to healthy controls resulted

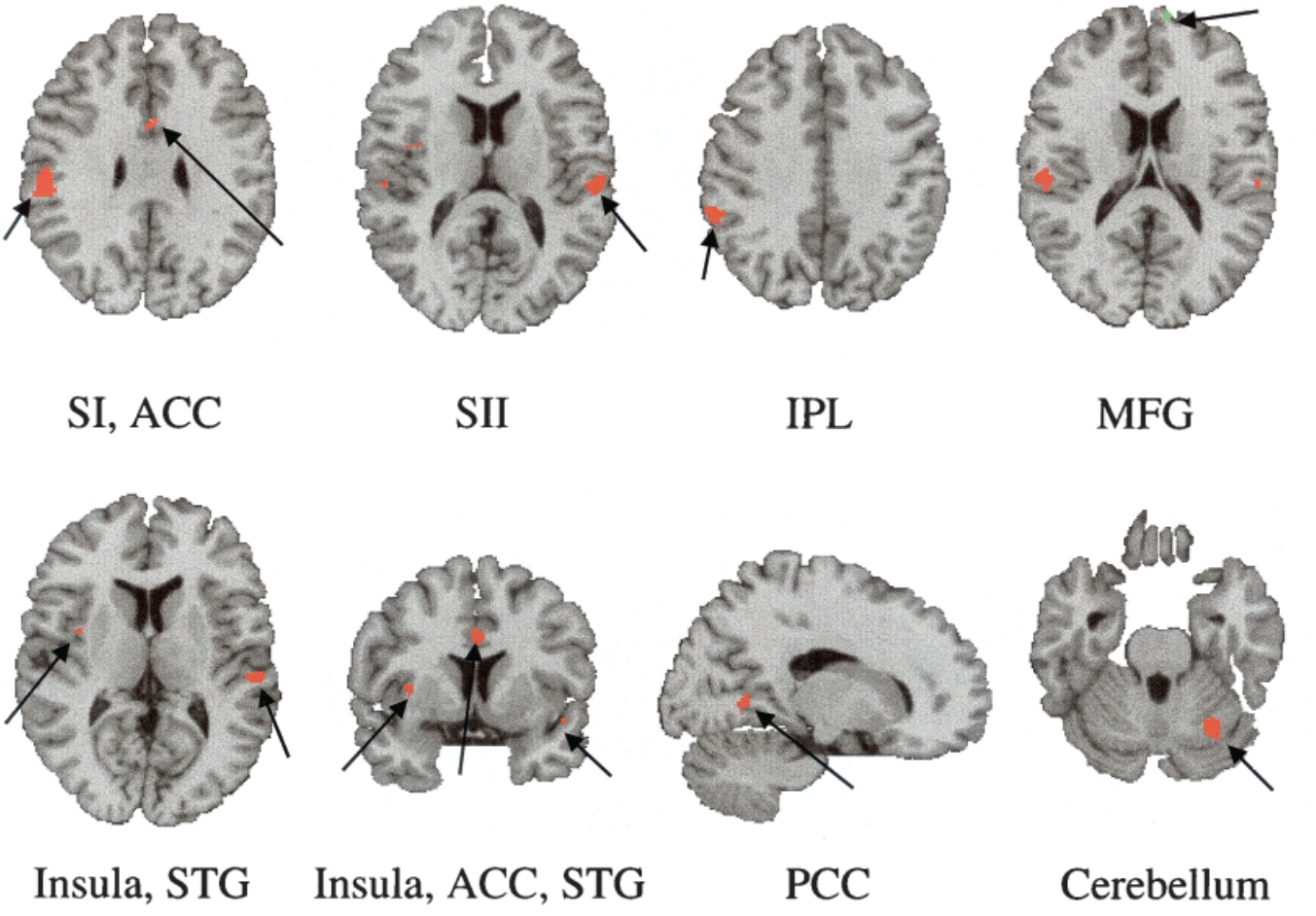

Figure 3. Comparison of the effects of similar stimulus pressures in patients and controls. Results of unpaired *t*-tests of the mean difference in signal (**arrows**) between painful pressure and innocuous touch for each group are shown in standard space superimposed on an anatomic image of a standard brain. Images are shown in radiologic view, with the right brain shown on the left. Regions in which the response in patients was significantly greater than the response in controls are shown in red; regions in which the response in controls was significantly greater than that in patients are shown in green. The level of significance was adjusted for multiple comparisons at $P < 0.05$. Patients showed significant activations that were significantly different from the activation in the healthy controls in the SI, IPL, insula, posterior cingulate cortex (PCC), SII, ATG, and cerebellum. The peak of the significant difference in anterior cingulate cortex (ACC) is in the right hemisphere, although the activation is near the midline and spreads into both hemispheres. Significant increases in the contralateral STG and in a second region of ipsilateral cerebellum are not shown. In contrast to these regions of significantly greater signal differences in patients, the similar stimulus pressures resulted in 1 region of significantly increased stimulus intensity in control subjects, located in the medial frontal gyrus (MFG). See Figure 2 for other definitions.

in 2 areas of significant activation; application of these same pressures to patients resulted in 12 areas of activation overall and 8 areas in common with those resulting from application of greater pressures to control subjects. This difference in the number of overall activations (12 versus 2) and common regions (8 versus 0) provides a second, qualitative line of evidence that pain sensitivity is augmented in patients with FM. The overlap in the similarly painful conditions and the enhanced response to lower stimulus intensities in patients provide converging lines of evidence for a mechanism involving central augmentation of pain sensitivity rather than simply a change in labeling behavior in the patient population. In terms of the initial experimental question, the result in patients more closely resembles the effects produced by the similar subjective pain magnitude condition in controls than the effects produced by the similar stimulus pressure condition in controls.

The enhanced response in somatosensory primary, secondary, and association areas and in the insula, putamen, and cerebellum contributes to the growing physical evidence of altered physiologic processing in

FM. These results are not consistent with simple psychological mechanisms of changed labeling behavior, in which patients establish a more liberal response criterion for reports of pain threshold and suprathreshold responses. However, it is important to note that proposed attentional mechanisms such as hypervigilance conceivably could have effects on the evoked cerebral response in sensory structures similar to those observed in this study.

Anticipation of a painful stimulus has been shown to increase activity in the secondary somatosensory cortex (34), and distraction has resulted in reduced activity in secondary and association somatosensory regions (35). Hypnotic suggestions have modulated activity in the primary sensory cortex (36) and in regions defined as "somatosensory areas" (37). However, no study of attentional or hypervigilance models has suggested the pattern of augmentation observed in this study, especially because we noted decreased activity in the anterior cingulate cortex, which shows increased activity during attention (38,39) and anticipation (34,40) and decreased activity during hypnotic analgesia (41,42). Previous studies have also demonstrated findings opposite to those in our FM patients, including increased activity in the thalamus during increased attention (39) or suggestions of analgesia (42) and increased activity in the insular cortex during anticipation of pain (34).

Thus, the available evidence suggests that the current results likely reflect the effects of noxious stimulation. The familiarization sessions and repetitive block design with internal control for innocuous stimulation likely minimized the effects of anxiety, and the use of long-duration stimuli may have minimized the role of anticipation. However, effects attributable to psychological factors such as attention, anticipation, and anxiety are potentially powerful and must always be considered in these types of experiments.

In addition to evidence consistent with augmentation of pain sensitivity in FM patients, the results also show evidence for attenuation of responses in FM patients compared with controls. In this study, patients did not show the increased response in the caudate nucleus that was observed in controls; this finding is consistent with the results of resting rCBF evaluation, which showed decreased basal flow in the caudate in FM patients (22). Painful stimulation in control subjects also resulted in significantly increased rCBF in a number of regions in the right and left thalamus; patients with FM showed no thalamic increases. Attenuated thalamic rCBF was also demonstrated in 2 studies of FM (22,23), 2 studies of neuropathic pain (43,44), and in a study of cancer-related pain (45). The studies of thalamic activity in FM showed low values of resting rCBF in the right thalamus and a similar trend in the left thalamus.

Although the evoked responses observed in the present study are consistent with results of resting rCBF evaluation, this consistency is not expected, nor is it necessary for validational support. Experimental determination of rCBF in the resting state should have little predictive value for evoked responses. Rather, comparing baseline flow with the changes evoked by an intervention may provide more information about underlying mechanisms than can be provided by either result in isolation. For example, reduced flow at baseline could permit a greater evoked response because of the classic physiologic law of initial values, in which the reduced baseline value permits a greater possible response up to a physiologic ceiling. Alternatively, reduced baseline flow might result from inhibitory processes that also attenuate evoked responses from the same region.

In the current study, findings of an attenuated increase of rCBF in contralateral (and possibly bilateral) caudate and bilateral thalamus in patients with FM, along with previous findings of lowered resting rCBF in these structures in FM patients, are consistent with a mechanism of tonic inhibition maintained by persistent excitatory input associated with ongoing and spontaneous pain. The viability of this mechanism is supported by the results of 2 studies that demonstrated decreased thalamic activity in pain attributable to mononeuropathy or cancer (43,45). In those experiments, in which pain was localized to a single extremity, analgesic treatment (regional nerve block to patients with neuropathic pain, percutaneous high cordotomy for patients with cancer pain) normalized the reduced rCBF observed in the contralateral thalamus, suggesting a process maintained by persistent painful input.

The increased spatial resolution of fMRI allows characterization of thalamic activations at the nucleic level. In previous studies, activation of the thalamus by painful stimuli was assumed to activate ventroposterolateral and ventroposteromedial regions corresponding to the termination of the pain projection system in the spinothalamic tract (44,46). The increased rCBF observed in this study localizes a subset of these activations to bilateral ventrolateral nuclei and contralateral ventroanterior nuclei, which are primarily involved in motor function. The presence of these thalamic activations solely in controls may represent an increased motor response that is part of the constellation of affective responses in healthy control subjects, or a number of alternative mechanisms. For example, the lack of activa-

tions in the thalamus in FM patients may reflect the lower stimulus intensity delivered to this group, suggesting that, in the presence of pain augmentation, information about stimulus magnitude may be preserved in specific components of the central nervous system. The observed motor activation is also consistent with ipsilateral activation, which could result from suppression of a "swat" response from the opposite upper extremity.

The high-pain condition in control subjects also resulted in a significant activation in the contralateral anterior nucleus. The anterior nucleus is an essential relay in the classic Papez (47) closed-loop limbic circuit, which involves a sequence of projections from the hippocampal formation to the mammilary bodies to the anterior nucleus. The anterior nucleus in turn projects to the cingulate cortex, which projects directly back to the hippocampal formation via the entorrhinal cortex or the septal nuclei. The prominent activation of the anterior nucleus in the high-pain control condition was accompanied by distinct but nonsignificant activations in the anterior cingulate in control subjects and significant difference between the control and patient groups in activations in the anterior cingulate by *t*-test comparison.

There is growing evidence that the anterior cingulate cortex is involved in processing the affective, unpleasant aspects of pain (19,39,41,48). Activation of a major input to the cingulate cortex solely in control subjects and significantly greater anterior cingulate activation in controls compared with patients, coupled with the unique activations in a variety of regions involved in motor responses (supplementary motor area, caudate, globus pallidus, ventrolateral, extensive cerebellar activations) observed in controls, suggest a state of reduced affective appraisal and responsiveness in FM. Decreased activations have been observed in several studies of chronic pain states (49–51). The lowered affective reactivity observed in the patient group is consistent with anecdotal evidence that, in the scanner, patients were actually more compliant than controls. Only data from control subjects had to be excluded because of excessive head motion. In addition, we have observed that a group of 43 FM patients found equally painful stimuli to be less unpleasant than did an age- and sex-matched control group of 28 subjects (52). These preliminary results and the putative role of the anterior cingulate cortex in processing pain unpleasantness suggest that the reduced response reflects an adaptive mechanism in which patients with chronic pain have become so accustomed to persistent pain that the brief, moderate-to-strong pain evoked in the experimental paradigm does not produce the emotional responses observed in those unaccustomed to such pain.

The present evidence of augmentation represents an initial step in the evaluation of the consequences and, ultimately, the causes of chronic pain syndromes such as fibromyalgia. The general augmentation observed in this experiment likely varies among individuals and may be mediated by multiple mechanisms and modulated by numerous factors that have been only partially identified. In addition, the current results can be classified as a static comparison of the consequences of painful mechanical stimulation in FM patients and matched control subjects. This static evidence provides a foundation for new studies that use dynamic designs to further characterize the differences observed in this study. These results compare groups under baseline conditions but do not compare the response of the groups to additional experimental manipulations. It is not known how the present results would be modified by interventions that address hypothetical mechanisms of FM. Dynamic designs that evaluate the effects of attention and external stressors and that challenge pain modulation systems will provide evidence for the mechanisms that mediate the spontaneous pain and evoked pain sensitivity that characterize FM and related disorders.

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