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Evidence of Augmented Central Pain Processing in Idiopathic Chronic Low Back Pain

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Objective. **For many individuals with chronic low back pain (CLBP), there is no identifiable cause. In other idiopathic chronic pain conditions, sensory testing and functional magnetic resonance imaging (fMRI) have identified the occurrence of generalized increased pain sensitivity, hyperalgesia, and altered brain processing, suggesting central augmentation of pain processing in such conditions. We compared the results of both of these methods as applied to patients with idiopathic CLBP (n = 11), patients with widespread pain (fibromyalgia; n = 16), and healthy control subjects (n = 11).**

Methods. **Patients with CLBP had low back pain persisting for at least 12 months that was unexplained by MRI/radiographic changes. Experimental pain testing was performed at a neutral site (thumbnail) to assess the pressure-pain threshold in all subjects. For fMRI studies, stimuli of equal pressure (2 kg) and of equal subjective pain intensity (slightly intense pain) were applied to this same site.**

Results. **Despite low numbers of tender points in the CLBP group, experimental pain testing revealed hyperalgesia in this group as well as in the fibromyalgia group; the pressure required to produce slightly intense pain was significantly higher in the controls (5.6 kg) than in the patients with CLBP (3.9 kg) ($P = 0.03$) or the patients with fibromyalgia (3.5 kg) ($P = 0.006$). When equal amounts of pressure were applied to the 3 groups, fMRI detected 5 common regions of neuronal activation in pain-related cortical areas in the CLBP and fibromyalgia groups (in the contralateral primary and secondary [S2] somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral S2). This same stimulus resulted in only a single activation in controls (in the contralateral S2 somatosensory cortex). When subjects in the 3 groups received stimuli that evoked subjectively equal pain, fMRI revealed common neuronal activations in all 3 groups.**

Conclusion. **At equal levels of pressure, patients with CLBP or fibromyalgia experienced significantly more pain and showed more extensive, common patterns of neuronal activation in pain-related cortical areas. When stimuli that elicited equally painful responses were applied (requiring significantly lower pressure in both patient groups as compared with the control group), neuronal activations were similar among the 3 groups. These findings are consistent with the occurrence of augmented central pain processing in patients with idiopathic CLBP.**

Chronic low back pain (CLBP) is one of the most common and expensive musculoskeletal disorders in developed countries (1,2). Back pain in general affects 70–85% of all people at some time in their lives, but 90% of affected individuals recover, typically within 12 weeks (3). Recovery after 12 weeks is slow and uncertain, and this subset of patients with CLBP accounts for major expenses in the health care and disability systems (2,4).

Despite the magnitude of the problem, little is known about the precise cause of CLBP. There is often a mismatch between objective findings and symptoms. Despite advances in imaging, in most patients, it is impossible to determine whether identifiable structural or mechanical abnormalities are responsible for the symptoms (5,6). Moreover, even when anatomic abnormalities are detected, the significance is unclear, since

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bulging disks or annular tears are found in high percentages of asymptomatic individuals (7,8).

This mismatch between anatomic abnormalities and symptoms has led to studies of the psychosocial factors that may contribute to CLBP. These studies suggest that increasing age, female sex, lower levels of formal education, depression, stress, job dissatisfaction, and disability/compensation issues may play some role in expression of symptoms and in chronicity (9–13). However, all of the known anatomic, demographic, and psychosocial factors that might cause CLBP do not explain the symptoms in a significant number of subjects (14,15). These individuals are sometimes referred to as having "idiopathic" or "nonspecific" CLBP.

Pain in other idiopathic chronic pain conditions, such as irritable bowel syndrome and fibromyalgia syndrome (FMS), appears to result from abnormalities in pain processing rather than from damage or inflammation of peripheral structures. A common finding in these and other "central" or "non-nociceptive" pain syndromes is increased tenderness to pressure, which can be classified as mechanical hyperalgesia (i.e., increased pain in response to normally painful stimuli) and/or mechanical allodynia (i.e., pain in response to normally nonpainful stimuli) (16,17). These abnormalities are found even in the absence of any identifiable psychological or behavioral factors, thus implicating central mechanisms that exacerbate pain (e.g., "wind-up") or that attenuate pathways that begin in the brain stem and normally inhibit the ascending transmission of pain-related activity (18–20).

The finding of augmented stimulation-evoked pain, assessed by patient self-report, has recently been corroborated by functional brain imaging techniques that allow the visualization of structures that are potentially involved in pain processing. These methods infer increased neural activity from highly localized increases in regional cerebral blood flow that are produced in response to anticipated metabolic demands. These methods can involve infusion of radioactive tracers (21,22) or, in the case of functional magnetic resonance imaging (fMRI), the magnetic character of the level of oxygen in the blood is used as an indirect, intrinsic tracer (23). Functional imaging studies have shown that painful stimulation produces increased neural activity in structures involved in the processing of sensation, movement, cognition, and emotion (22,24,25). Functional imaging studies in chronic pain states that are characterized by hyperalgesia/allodynia have corroborated patients' self-reports of mechanical hyperalgesia, identifying objective evidence of augmented responses to pressure stimuli (such as in the viscera and periphery in irritable bowel syndrome and FMS, respectively) (26,27).

In a recent cross-sectional study of CLBP, we demonstrated that a simple laboratory measure of pressure-pain sensitivity was the best correlate of pain and functional status, exceeding the predictive value of any other demographic, psychological, or radiographic variable (15). In the present study, we have expanded on this work and performed both experimental pain testing and functional imaging in a cohort of patients with CLBP. This particular cohort was specifically identified to have idiopathic CLBP, i.e., individuals without evidence of any anatomic abnormalities on MRI or plain radiographs that could explain these symptoms. These patients were compared with both a normal healthy control group and a cohort of individuals with FMS.

PATIENTS AND METHODS

Patients and control subjects. The study was conducted at Georgetown University Hospital, and patients were recruited from tertiary care spine and fibromyalgia centers. Sixteen right-handed adult patients scheduled for a visit for low back pain were recruited from a sample of consecutive clinic patients. The inclusion criterion in this group was that low back pain be the dominant symptom. In accordance with the generally accepted definition of CLBP (28), the duration of pain had to be at least 12 weeks. Idiopathic low back pain was diagnosed according to the guidelines and exclusion criteria recommended by Deyo and Weinstein (1). These exclusion criteria included pain in areas other than the lower back, evidence of a fracture (including vertebral fractures due to osteoporosis) or malignancy that may account for the pain, inflammatory joint disease, or previous neck or back surgery.

Radiographs and MRI scans of the spine were obtained and evaluated by a physician (AN) who was not familiar with either the patients or the results of testing. The radiographs were graded using the system developed by Weiner and colleagues (29), and the MRI scans were graded using the technique described by Videman and colleagues (30). There is no rating scale for radiographic or MRI studies that is perfect in estimating the degree of patho-anatomic abnormality in CLBP. We concluded that the above-noted standardized approaches were the best of those published, and that it would be preferable to use these established methods rather than design a unique scale for use in this study.

Seventeen right-handed patients (13 women, 4 men; mean $\pm$ SD age 45 $\pm$ 12 years) who met the 1990 American College of Rheumatology (ACR) criteria for FMS (31) at the time of the study were randomly selected from a sample of consecutive clinic patients. These patients formed the FMS group. In addition, 15 right-handed, healthy subjects were recruited through newspaper advertisements and were compensated for their participation; these subjects served as controls.

Subjects were screened by a medical history review and physical examination. General exclusion criteria for all subjects were severe physical impairment (e.g., bilateral amputation,

complete blindness or deafness), medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases), cardiopulmonary disorders (i.e., angina, congestive heart failure, chronic obstructive pulmonary disease, chronic asthma), chronic renal insufficiency, uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., current schizophrenia, substance abuse within 2 years), factors known to affect the hypothalamic–pituitary–adrenal axis or autonomic function (cigarette smoking, daily intake of caffeine exceeding the equivalent of 2 cups of coffee), and medication usage other than as-needed analgesics (excluding long-term narcotics) and appropriate dosages of thyroid hormone. Patients were asked to discontinue intake of antidepressants up to 4 weeks ahead of the appointment (depending on the half-life of the drug), but were allowed to take nonsteroidal antiinflammatory drugs until 3 days before the baseline psychophysical evaluation and the fMRI sessions. Patients receiving long-term opioid medications were excluded.

All subjects gave their written informed consent before testing. The protocol was approved by the Georgetown University Institutional Review Board.

Self-report questionnaires. *Center for Epidemiological Studies Depression Scale (CES-D).* The CES-D is an extensively evaluated 20-item instrument that has good psychometric properties and strong associations with other measures of depressive symptoms (32).

State-Trait Personality Inventory (STPI). A 20-item subset of the STPI (Form Y) was used to assess trait anxiety. These items of the STPI have been well-validated as part of larger instruments, such as the State-Trait Anxiety Inventory and the State-Trait Anger Inventory (33).

*Pain location.*To determine each subject's distribution of pain, we administered a graphic display representing the front and back of the body (34). To quantify the results, the front of the body was divided into 34 symmetric sections plus the eyes and groin, and the back was divided into 26 symmetric sections plus the anus/rectum. Each section contained a corresponding circle. Subjects were asked to indicate the sections in which they typically experienced pain by filling in the corresponding circle. They were instructed to fill in as many circles as applicable to the areas where they typically experienced the pain.

Clinical pain. The experience of clinical pain in subjects was assessed using the Short-Form of the McGill Pain Questionnaire (SF-MPQ) (35). This questionnaire has been extensively evaluated and contains 15 pain adjectives. A sensory score is obtained by summing 11 of the items, an affective score is obtained by summing the remaining 4 items, and a total score is obtained by summing all of the items.

Experimental pain assessment. In a pre-fMRI baseline session, a well-trained and experienced research assistant performed the manual tender point count. Pressure was applied with the dominant thumb at the locations defined by the ACR criteria. Pressure was increased by 1 kg/second up to 4 kg, while making a rotating, massaging movement with the thumb. After the pressure was released, the patient was asked: "Was that painful?"

The tender point count was followed by a determination of pressure-pain sensitivity by subjective scaling of multiple pressure-pain sensations of suprathreshold intensities. Discrete, 5-second pressure stimuli were applied with a 1-cm^2 hard rubber probe to the fixated left thumbnail. Previous studies have shown that "neutral" regions such as the thumb accurately reflect an individual's overall pressure-pain sensitivity (36). The rubber probe was attached to a hydraulic piston, a combination of valves (to control stimulus duration), and a scale. Calibrated weights were placed on the scale to produce controlled, repeatable pressure-pain stimuli of rectangular waveform at the thumbnail. Subjects rated the intensity of pressure-pain sensations using a combined numeric analog descriptor scale, developed from previously quantified verbal descriptors (37). First, a series of stimuli was presented in a predictable, "ascending" manner, beginning at 0.5 kg/cm^2 and increasing in 0.5-kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2. Following the ascending series, 36 stimuli were delivered at 20-second intervals in random order, using the multiple random staircase (MRS) method (38). The MRS method is response-dependent, i.e., it determines the stimulus intensity needed to elicit a specified response.

Functional imaging. MRI and fMRI scans were performed on a 1.5-Tesla vision system (Siemens, Munich, Germany). A T1-weighted MRI anatomic scan session (time to echo [TE] 4 mseconds, time to recovery [TR] 9.7 mseconds, flip angle 12°, 256 × 256-pixel matrix, field of vision [FOV] 256 mm, 1-mm^3 voxels acquired noninterleaved in the sagittal direction) was followed by 2 functional scan sessions using multislice echo-planar imaging fMRI acquisition (TE 40 mseconds, 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 within 5 seconds.

During each functional scan session, the whole brain was scanned 128 times. Three initial scans allowed for saturation of the tissue. Starting on the fourth scan, pressure stimuli of 25 seconds' duration ("on" condition) were alternated with 25-second resting periods ("off" condition). Onset and offset of a stimulus was always coincident with the beginning of a scan, allowing the acquisition of 5 scans during each "on" condition and each "off" condition.

During the "on" condition, different stimulus intensities were presented in a random manner. These stimulus intensities included three 2-kg stimuli that constituted the equal pressure condition, and 3 stimuli, chosen on the basis of the baseline pain testing, that were sufficient to elicit a rating of 13.5 of 20 units (slightly intense pain), thus constituting the equal pain condition. The analysis was performed on the scans acquired during the equal pressure condition, the equal pain condition, and the "off" conditions.

Statistical analysis. Statistical analyses were performed using SPSS for Windows (SPSS, Chicago, IL). Group comparisons with not normally distributed data (tender point counts, duration of symptoms, body mass index) were performed using the Kruskal-Wallis test. Normally distributed data were compared using one-way analysis of variance, followed by Gabriel's procedure when variances were found equal, and by the Games-Howell procedure when variances were unequal. Homogeneity of variances was tested using Levene's test. A P value of less than 0.05 was generally considered significant.

Table 1. Group characteristics and results of pressure-pain testing*

	Healthy controls (n = 11)	CLBP patients (n = 11)	FMS patients (n = 16)
Demographic			
Sex no. male/no. female	7/4	3/8	4/12
Age, years	41 ± 7	44 ± 13	45 ± 12
Median (range) BMI, kg/m^2	25 (20–30)	24 (17–32)	28 (21–36)
Median (range) duration of symptoms, months	–	54 (12–312)	86 (12–300)
No. of pain locations (maximum 63)	0.8 ± 1.4	10.1 ± 6.0†	32.4 ± 9.8‡
No. of tender points	3.2 ± 5.3	3.3 ± 3.2	15.1 ± 2.9‡
Depressive symptoms score on CES-D	4.8 ± 5.9	11.5 ± 7.5	17.8 ± 11.9‡
Anxiety score on STPI	15 ± 4.4	18.5 ± 4.4	21.8 ± 7.3†
Clinical pain			
SF-McGill sensory	0	6.2 ± 5.7‡	8.5 ± 5.2‡
SF-McGill affective	0	1.6 ± 1.7‡	2.3 ± 1.8‡
SF-McGill total	0	7.8 ± 6.9‡	10.8 ± 6.3‡
Pain testing results			
Pain threshold, kg	2.7 ± 2.1	0.7 ± 0.5§	0.7 ± 0.5§
Moderate pain, kg	5.3 ± 2.8	2.7 ± 2.7§	2.2 ± 1.4†
Slightly intense pain, kg	7.3 ± 1.7	4.9 ± 2.4§	4.1 ± 2.5†
fMRI scanner results			
Equal pressure, kg	2.0	2.0	2.0
Pain intensity rating (maximum 20)	1 ± 1.1	6 ± 4.2§	6 ± 4.2§
Equal pain intensity, kg	5.6 ± 1.7	3.9 ± 1.3§	3.5 ± 1.6†
Pain intensity rating (maximum 20)	14 ± 3.8	16 ± 1.5	16 ± 2.3

* Values are the mean ± SD, except where indicated otherwise. CLBP = chronic low back pain; FMS = fibromyalgia syndrome; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; STPI = State-Trait Personality Inventory; SF-McGill = Short-Form of the McGill Pain Questionnaire; fMRI = functional magnetic resonance imaging.
† $P < 0.01$ versus healthy controls.
‡ $P < 0.001$ versus healthy controls.
§ $P < 0.05$ versus healthy controls.

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 brain volumes collected during equal pressure and equal pain conditions were compared with the brain volumes collected during "off" conditions by *t*-test, and a Z-map (with a Z score for each voxel) was created for each subject. The Z score is a value that indicates a distribution, with a mean of zero, and each integer indicates a standard deviation of 1 (e.g., a Z score of 2 indicates 2 SD above the mean, a Z score of −3 is 3 SD below the mean). Results for fMRI are commonly presented as Z scores. Resultant Z-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 of both functional runs divided by the square root of the number of scans. Activations were considered significant at a *P* value less than 0.05, corrected for multiple comparisons using the random Gaussian field theory correction (39). The search volume consisted of "pain-relevant" regions determined in previous studies (27).

Anatomic regions were identified by the following: 1) inspection of individual functional images superimposed on an individual structural image, and 2) conversion of the coordinates to the coordinate system of the Talairach-Tournoux Atlas and localization using this Atlas (40) and automated software (41).

RESULTS

After grading the radiographs and MRI scans, 2 patients with disc extrusion, 1 patient with spinal stenosis, and 1 patient with spondylolisthesis were excluded from the CLBP group because of possible neural compromise. Of the remaining 12 patients with CLBP, 6 were assigned a global assessment grade of 1 from their radiographs (scale 1–4), with maximum grade 1 disc degeneration from L3 to S1. Six patients with CLBP had a global assessment grade of 2, with grade 2 to grade 3 disc degeneration from L3 to S1. In the MRI evaluations, none of the patients with CLBP had disc protrusion or any other visible cause of neural compromise, none had a disc-height reduction of more than 50%, and none had more than grade 1 endplate degeneration (scale 0–3).

One patient with CLBP declined to undergo the fMRI procedure, and for 1 patient with FMS and 4 control subjects, the imaging results for both conditions could not be interpreted because of excessive head motion. Therefore, the data for these 6 subjects were

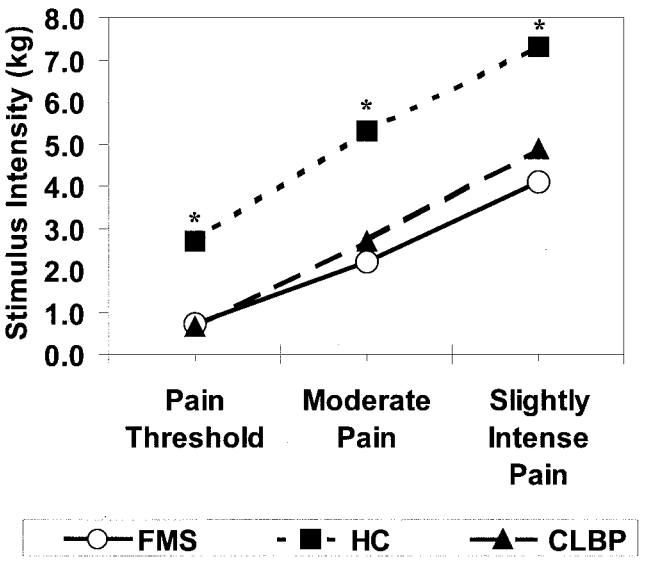

Figure 1. Stimulus-response functions in all 3 groups, obtained by psychophysical pain testing using the multiple random staircase paradigm. Stimulus intensities for pain thresholds and suprathreshold stimuli sufficient to elicit a rating of moderate pain (7.5 of 20 units on the Gracely pain box scale) and slightly intense pain (13.5 of 20 units on the Gracely pain box scale) are shown for each group. Both the chronic low back pain (CLBP) and fibromyalgia syndrome (FMS) patient groups show a significant lowering of the stimulus response, with almost identical slopes. HC = healthy controls. $* = P < 0.05$ versus patient groups.

excluded from the analysis. Eleven patients with CLBP, 16 patients with FMS, and 11 control subjects formed the final study population. Table 1 shows the characteristics of the 3 study groups.

The ethnic representation was comparable in the groups. The CLBP group and the control group each had 8 whites (73%), 2 African Americans (18%), and 1 Hispanic (9%). The FMS group had 11 whites (69%), 3 African Americans (19%), and 2 Hispanics (13%).

Both patient groups reported significantly more clinical pain on the SF-MPQ as compared with that reported by the controls. However, there was no significant difference in the level of clinical pain between the patients with CLBP and those with FMS. These results are shown in Table 1.

Table 1 also shows the expected greater extent of pain, measured by a pain body map, in the patients with FMS (mean 32.4 sites indicated as painful, of a possible 63 body sites) compared with that in the patients with CLBP (mean 10.1 sites indicated as painful, mainly in the low back) and healthy controls (mean 0.8 sites indicated as painful). As expected, the patients with FMS also reported greater numbers of tender points (mean ± SD 15.1 ± 2.9, of 18 possible), whereas the tender point counts were nearly equal between the CLBP group (mean 3.3) and healthy controls (mean 3.2).

Similar to the differences in the tender point count, the FMS group displayed significantly higher levels of psychological distress than did the healthy control group, as measured by their depression and anxiety scores. Although there was a trend toward higher levels of anxiety and depression in the CLBP group, neither the difference from the patients with FMS nor the difference from the healthy control group was statistically significant.

The results of the more sophisticated experimental pain-testing procedures are also shown in Table 1. Despite the higher tender point counts in the patients with FMS, both patient groups displayed similar pain

Table 2. Areas of neuronal activations at the equal pressure (2 kg) condition*

Side, cortical region, group	x	y	z	Z score
Contralateral				
Primary somatosensory				
CLBP	57	−13	43	7.73632
FMS	59	−15	43	5.15532
Secondary somatosensory				
HC	61	−18	21	4.20553
CLBP	55	−22	18	7.23976
FMS	65	−28	16	5.02477
Ipsilateral				
Secondary somatosensory				
CLBP	−65	−15	12	5.86164
FMS	−59	−17	10	4.77318
Inferior parietal				
CLBP	46	−44	56	4.45876
FMS	40	−46	59	4.44034
Cerebellum				
CLBP	−32	−57	−21	3.55417
FMS	−30	−56	−22	5.27124

* Values for x, y, and z are standard coordinates (in mm) in the 3-dimensional Talairach space (40). CLBP = chronic low back pain; FMS = fibromyalgia syndrome; HC = healthy controls.

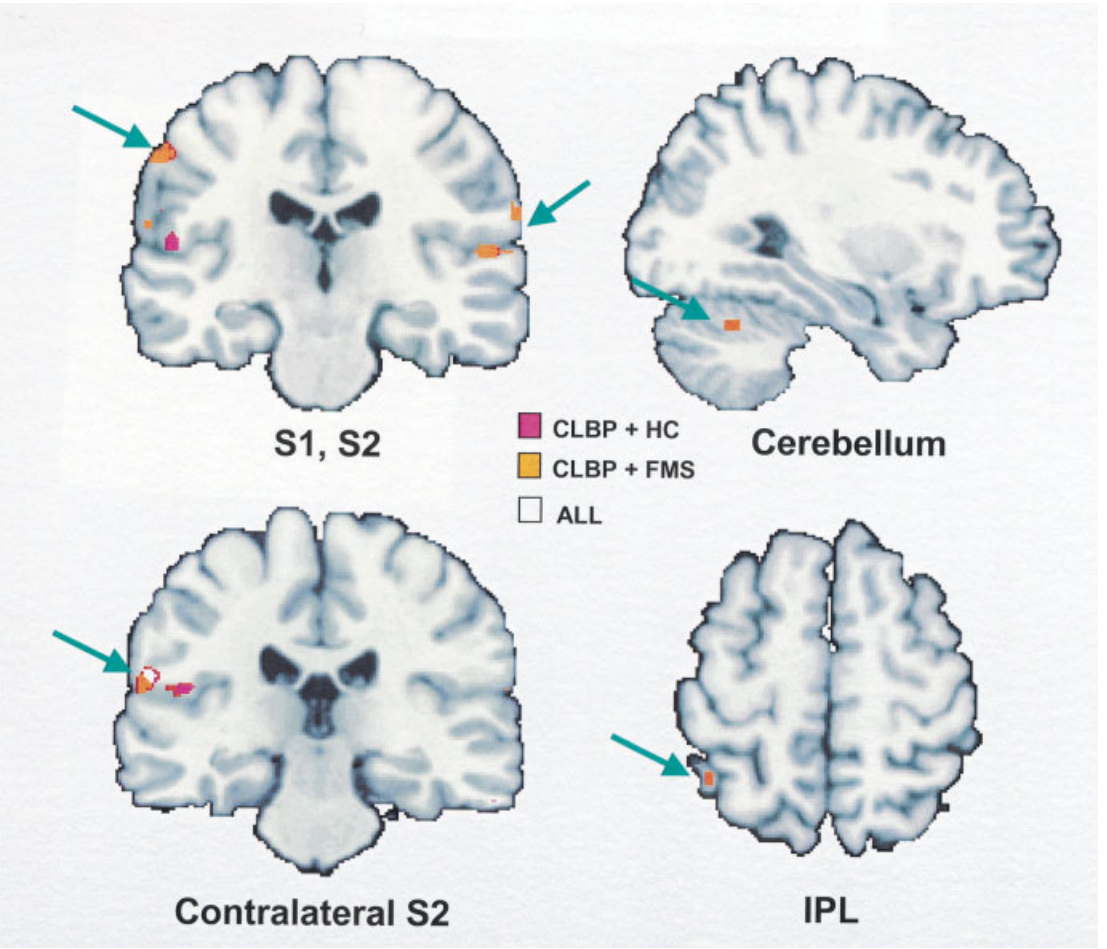

Figure 2. Overlapping neuronal activations under the equal stimulus condition. In the chronic low back pain (CLBP), fibromyalgia syndrome (FMS), and healthy control (HC) groups under the equal pressure condition, significant increases in pain-related neuronal activations **(arrows)** are demonstrated in standard space superimposed on a structural T1-weighted magnetic resonance image. Images are shown in radiologic view, with the right brain shown on the left. Overlapping activations appear in the indicated colors. Equal pressure intensities result in 5 overlapping areas of neuronal activation in the CLBP and FMS groups (in the contralateral S1, S2, and inferior parietal lobule [IPL], and in ipsilateral S2 and cerebellum), but in only 1 overlapping area of neuronal activation among the HC, CLBP, and FMS groups (in the contralateral S2).

thresholds at the left thumb and these were significantly lower than that of the healthy control group. Similarly, the suprathreshold pressure intensities sufficient to evoke moderate or slightly intense pain were significantly lower in the patient groups compared with the healthy control group (Figure 1).

Correspondingly, pressure intensities adapted to evoke slightly intense pain on the fMRI scanner were significantly lower in both patient groups than in the control group (mean ± SD pressure intensity in patients with CLBP 3.9 ± 1.3 kg, patients with FMS 3.5 ± 1.6 kg, and healthy controls 5.6 ± 1.7 kg; $P < 0.05$). Pain intensity ratings obtained immediately after each scanning session confirmed that these stimuli evoked equally painful sensations (mean ± SD [of a maximum 20] pain intensity rating in patients with CLBP 15.8 ± 1.5, patients with FMS 15.8 ± 2.3, and healthy controls 14.3 ± 3.8). Figure 1 displays the similar lowering of pain thresholds in both patient groups as compared with the healthy control group.

The fMRI analyses of the response under the equal pressure condition revealed that in both the patients with CLBP and patients with FMS, 2 kg pressure resulted in ratings of moderate pain and led to an increase in the fMRI signal in the contralateral primary (S1) and secondary (S2) somatosensory cortices, ipsilateral S2, inferior parietal lobule (IPL), and cerebellum. In contrast, this same 2-kg stimulus in the healthy control group produced a rating of only faint pain and resulted in an increase in the fMRI signal in only the contralateral S2 cortical region. Table 2 shows the

Table 3. Areas of neuronal activations under the equal pain condition (slightly intense pain)*

Side, cortical region, group	x	y	z	Z score
Contralateral				
Primary somatosensory				
HC	57	−27	46	4.0843
CLBP	57	−19	42	7.94725
FMS	57	−13	43	5.39763
Secondary somatosensory				
HC	55	−21	12	4.59193
CLBP	61	−15	14	7.72307
FMS	65	−22	18	6.56891
Inferior parietal lobule				
HC	53	−44	50	3.60315
CLBP	51	−46	48	3.7111
FMS	42	−40	48	3.70678
Insula				
HC	50	−23	16	4.58386
CLBP	48	−24	20	5.9398
FMS	40	2	9	5.06572
ACC				
HC	2	4	46	3.86455
CLBP	2	12	42	3.94788
FMS	2	18	40	3.87204
Ipsilateral				
Secondary somatosensory				
HC	−69	−17	19	6.09707
CLBP	−63	−17	12	7.51685
FMS	−67	−17	10	6.88006
Cerebellum				
HC	−36	−65	−22	6.11633
CLBP	−34	−59	−21	5.44895
FMS	−34	−61	−22	7.10124

* ACC = anterior cingulate cortex (see Table 2 for other definitions).

anatomic locations, standard coordinates, and Z scores for these neuronal activations. Figure 2 shows the areas of overlapping activation in the brain.

In contrast to the results obtained at equal pressure intensities, all 3 groups tested under the equal pain condition (slightly intense pain) showed significant increases in the fMRI signal in the contralateral S1, S2, IPL, insula, and anterior cingulate cortex (ACC), and in ipsilateral S2 and cerebellum. Table 3 shows the anatomic locations, standard coordinates, and Z scores for these neuronal activations under equal pain. Figure 3 shows the areas of overlapping activation in the brain.

Although the groups were not significantly different with regard to age, there was a sex mismatch between the control group and the patient groups. To ensure that our results were not due to this imbalance in the sexes, we evaluated the association of sex with the individual pain thresholds as well as the individual mean differences between the equal pressure condition, the equal pain condition, and the "off" conditions of the fMRI experiment. In addition, we performed *t*-tests of pain thresholds and fMRI mean differences between men and women in all 3 groups. No significant correlations were found between sex and any of these variables (r = 0.12–0.25, P = 0.4–0.7). Likewise, none of the *t*-tests showed any significant differences in pressure sensitivity or fMRI signal between the men and the women within the groups.

DISCUSSION

The experimental pain testing performed in this study suggests that a subset of individuals with idiopathic CLBP have increased pressure-pain sensitivity at a site distant from their region of clinical pain (in this case, the thumb). Functional MRI, which allows visualization of changes in regional cerebral blood flow associated with the application of painful stimuli, corroborated the fact that patients with CLBP were more sensitive to pressure stimuli than were control subjects. The pain amplification was also found in the patients with fibromyalgia in this study, confirming previous fMRI findings in patients with fibromyalgia (27). Central pain amplification has further been noted in other idiopathic chronic pain syndromes, such as irritable bowel syndrome (26). Our results extend this finding of central pain amplification to a group of individuals with chronic regional peripheral pain syndromes such as low back pain.

In the healthy control subjects, a pressure stimulus of 2 kg applied on the left thumb evoked only faint pain and resulted in a significant increase of neural activation in the contralateral S2 cortical region only. Activations in S2 are commonly found during painful stimulation (42), but are not specific to the evoked pain. Activity in S2 has been described after nonpainful tactile (43), electrical (44), and vibratory stimulation (45), and thus S2 is considered to be a somatosensory integrative area.

In the patients with CLBP and patients with FMS, however, applying the same 2 kg of pressure, which both groups rated as being moderately painful, resulted in numerous significant neural activations of pain-related brain areas. In addition to the contralateral S2, the stimulus also caused significant increases in the fMRI signal in the ipsilateral S2 and cerebellum, and in the contralateral S1 and IPL. These regions of the brain have all been implicated in pain processing with functional roles, such as stimulus identification and encoding (S1), attention (IPL), and motor response (cerebellum).

In contrast to the findings under the equal pressure condition, the equal pain condition resulted in qualitatively similar activations of the contralateral S1 and S2, ipsilateral S2, cerebellum, and the contralateral IPL in all 3 groups. The magnitude of these activations, however, was still greater in the CLBP and FMS groups. Furthermore, in all 3 groups, we observed similar acti-

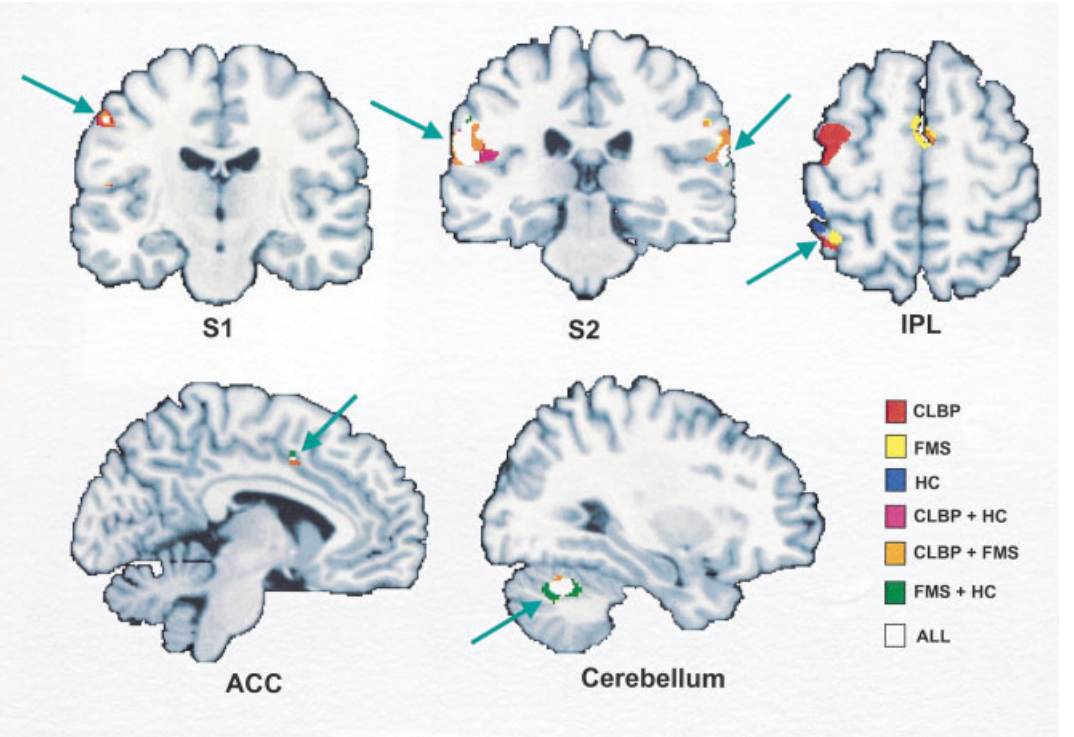

Figure 3. Overlapping neuronal activations under the equal pain condition. In the CLBP, FMS, and HC groups under the equal pain condition, significant increases in pain-related neuronal activations **(arrows)** are demonstrated in standard space superimposed on a structural T1-weighted magnetic resonance image. Images are shown in radiologic view, with the right brain shown on the left. Overlapping activations appear in the indicated colors. Equal subjective pain intensities result in 7 overlapping or adjacent areas of neuronal activation among the CLBP, HC, and FMS groups (in the contralateral S1, S2, and IPL, anterior cingulate cortex [ACC], insula [not shown], and in ipsilateral S2 and cerebellum). See Figure 2 for other definitions.

vations of the contralateral ACC, another area that has been associated with perceived pain intensity (46).

Another significant neuronal activation in all 3 groups was observed in the contralateral insula. However, whereas the activations in the CLBP and healthy control groups were correspondingly located in the posterior insula, the activation in the FMS group was located in a more anterior-inferior position. Although frequently seen in pain studies, neither anterior nor posterior insular responses are specific to pain (42). Activation of the posterior insula has mostly been observed as being associated with activation of S2, and very often both activations overlap (21,45,47). The anterior insula is consistently activated in emotional tasks with negative affective components, such as tasting salt (48) or viewing faces of disgust (49). The anterior insular activation in the patients with FMS may indicate a stronger affective response to the pain stimuli, which in turn may be associated with their higher level of distress.

The enhanced response in the S1, S2, IPL, and cerebellum contributes to the growing physical evidence of altered physiologic processing in chronic pain conditions such as CLBP and FMS. The association of CLBP with a central disturbance in pain processing is congruent with findings in other chronic pain states. Increased pain sensitivity outside the areas of clinical pain has been reported for other regional pain syndromes, such as tension-type headache (50), temporomandibular disorder (51,52), and localized trapezius myalgia (18). Our findings are also consistent with those of other studies that have demonstrated lowered pain thresholds in patients with low back pain (53) and lowered thresholds in patients with regional or widespread pain who do not have the 11 tender points required for the diagnosis of fibromyalgia (54).

These results are also consistent with other functional imaging studies that have suggested augmented central pain processing in chronic pain conditions, including fibromyalgia (27,55), irritable bowel syndrome (26), cerebral infarction complicated by allodynia (56), and atypical facial pain (57). In the only previous study that used functional neuroimaging to assess patients

with low back pain, Derbyshire et al used positron emission tomography to compare cerebral responses to heat stimulation in patients with CLBP and healthy control subjects (58). That study found similar stimulus encoding between groups, but did not examine differences in response to equally painful stimuli or test differences in absolute response to equally intense stimulation.

It is interesting to note that typical clinical testing would not have detected the central pain amplification in the CLBP group. The most common clinical test used to detect diffuse tenderness is a tender point count. This cohort of patients with CLBP had normal numbers of tender points, and they were experiencing pain primarily in the axial region, particularly the low back. Thus, they were quite different clinically from the individuals with fibromyalgia, whose condition was characterized by chronic widespread pain and the presence of $\geq$11 (of 18) tender points. However, when we evaluated the pressure-pain sensitivity at a site distinct from their region of pain (in this case, the thumbnail), the patients with CLBP demonstrated increased tenderness similar to that of the patients with FMS, who were tested in the same manner.

The disparity between the tender point count and the more sophisticated measures of tenderness is likely due to external factors that influence easily biased methods such as the tender point count (38,59). Wolfe first noted the discrepancy between tender point counts and other measures of tenderness, and also observed that tender point counts are highly correlated with distress, prompting the suggestion that tender points are a "sedimentation rate for distress" (59). Subsequent studies have confirmed the influence of distress on clinical measures such as the tender point count, and the lack of such influence on paradigms using random stimulus application (60). As shown in Table 1, both the levels of depressive symptoms and the extent of anxiety were higher in the FMS group than in the CLBP group, so this higher level of distress could have accounted for the relatively higher tender point count in the FMS group. It is also possible that patients with FMS "learn" that tender points are areas where they are supposed to be more tender, and thus report higher levels of pain on palpation of these regions (61).

The present evidence of central pain augmentation represents an initial step in the evaluation of potential central nervous system contributions to chronic pain syndromes such as idiopathic CLBP and fibromyalgia. Pressure-pain sensitivity is the hallmark symptom of fibromyalgia, and several lines of experimental evidence suggest that it is centrally mediated. Recent studies suggest that many other regional pain syndromes may likewise have primarily a central, rather than a peripheral, basis, including not only irritable bowel syndrome, but also temporomandibular syndrome, noncardiac chest pain, and interstitial cystitis, among others. This spectrum of illness goes by many different semantic terms (e.g., functional somatic syndromes, somatoform disorders), and while the precise cause remains unknown, there is unanimity that these are very common symptoms and syndromes (62–64).

Preliminary studies such as this need replication and extension. In addition to the small sample size in this study, other possible problems are the recruitment of subjects from tertiary care centers and newspapers, and the fact that we did not control for the menstrual cycle of the women. Nevertheless, if the symptoms in a substantial number of individuals with CLBP are due to abnormal central pain processing rather than due to damage or inflammation of peripheral structures, this would have enormous clinical implications. These data suggest that the individual pain threshold should be evaluated in clinical practice. The finding of a low pressure-pain threshold at neutral sites (e.g., the thumbnail) might indicate a central, rather than peripheral, cause for the pain.

This information presented in this study may guide treatment strategies. Drugs that affect central levels of neuromodulators known to be involved in pain processing (e.g., tricyclic antidepressants) are more effective in the management of centralized pain than are alternate classes of compounds that work well for peripheral pain (e.g., nonsteroidal antiinflammatory drugs or opioids) (63,65). Similarly, nonpharmacologic therapies, such as aerobic exercise and cognitive behavioral therapy (66), can be especially useful adjuncts to treating this constellation of chronic pain symptoms and syndromes.

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