THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Vol. 98, No. 6, 2003

Published by Elsevier Inc.
ISSN 0002-9270/03/$30.00
doi:10.1016/S0002-9270(03)00253-3

Brain Responses to Visceral and Somatic Stimuli in Patients With Irritable Bowel Syndrome With and Without Fibromyalgia

Lin Chang, M.D., Steve Berman, Ph.D., Emeran A. Mayer, M.D., Brandall Suyenobu, Ph.D., Stuart Derbyshire, Ph.D., Bruce Naliboff, Ph.D., Brent Vogt, Ph.D., Leah FitzGerald, R.N., and Mark A. Mandelkern, M.D., Ph.D.

C.N.S. Center for Neurovisceral Sciences & Women's Health, Departments of Medicine, Physiology, and Psychiatry & Biobehavioral Sciences, and Brain Research Institute, David Geffen School of Medicine at UCLA, Los Angeles, California; University of Pittsburgh Medical Center, MR Research Facility, Pittsburgh, Pennsylvania; Cingulum NeuroSciences Institute, Syracuse, New York; GLA VA Healthcare System, Department of Nuclear Medicine, Irvine; and Departments of Biomathematics & Biostatistics and Physics, University of California, Irvine, California

OBJECTIVE: Symptoms of irritable bowel syndrome (IBS) and fibromyalgia (FM) commonly coexist. We hypothesized that one of the mechanisms underlying this comorbidity is increased activation of brain regions concerned with the processing and modulation of visceral and somatic afferent information, in particular subregions of the anterior cingulate cortex (ACC).

METHODS: Regional cerebral blood flow (rCBF) was assessed in age-matched female IBS ($n = 10$) and IBS + FM ($n = 10$) subjects using $H_2{}^{15}O$ positron emission tomography during noxious visceral (rectal) and somatic pressure stimuli.

RESULTS: GI symptom severity was significantly higher in the IBS patients compared with the IBS + FM patients ($p < 0.05$). In addition, IBS + FM patients rated somatic pain as more intense than their abdominal pain ($p < 0.05$). Whereas the somatic stimulus was less unpleasant than the visceral stimulus for IBS patients without FM, the somatic and visceral stimuli were equally unpleasant in the IBS + FM group. Group differences in regional brain activation were entirely within the middle subregion of the ACC. There was a greater rCBF increase in response to noxious visceral stimuli in IBS patients and to somatic stimuli in IBS + FM patients.

CONCLUSION: Chronic stimulus-specific enhancement of ACC responses to sensory stimuli in both syndromes may be associated with cognitive enhancement of either visceral (IBS) or somatic (IBS + FM) sensory input and may play a key pathophysiologic role in these chronic pain syndromes. (Am J Gastroenterol 2003;98:1354–1361. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Irritable bowel syndrome (IBS) and fibromyalgia (FM) are syndromes characterized by chronic visceral and chronic somatic pain and discomfort, respectively. Patients affected by both disorders are commonly seen in tertiary referral centers for functional GI disorders and frequently pose a considerable therapeutic challenge. Epidemiologic studies have confirmed the clinical impression that these two functional disorders frequently overlap in the same patient, suggesting shared pathophysiologic mechanisms (1). A study of 80 patients demonstrated that 70% of FM patients also had symptoms of IBS, and 65% of IBS patients suffered from FM symptoms (2). Although unequivocal demonstration of peripheral tissue changes underlying the pain is lacking in both syndromes, local pain elicited at known tender points is considered the hallmark physical finding of FM, whereas tenderness of the sigmoid colon during palpation or endoscopic manipulation is characteristic in IBS. In IBS, several studies have demonstrated lower perceptual thresholds for pain and discomfort during colorectal balloon distension (3–5). In FM, several studies have demonstrated decreased pain thresholds both at tender points and at control sites (6–12).

Although the pathophysiology for both conditions is incompletely understood, an alteration in central nervous system (CNS) function has been suggested by several observations in both conditions: 1) the majority of patients associate stressful life events with the initiation or exacerbation of symptoms (13, 14), 2) psychotherapy and behavioral therapies (including hypnotherapy and relaxation techniques) are efficacious in treating symptoms (15–17), 3) low-dose tricyclic antidepressant medication can improve symptoms of FM (18, 19) and IBS (20), most likely by their CNS-mediated effect (21–23), and 4) altered regional cere-

bral responses to visceral and somatic stimulation have been demonstrated in FM (24) and IBS (24–26). Consistent with such a CNS-based shared pathophysiology, Whitehead *et al.* recently suggested, based on an extensive review of published studies, that the strong comorbidity between IBS and FM suggests a common psychological feature important to their expression (1).

Because visceral and somatic afferents are jointly processed and modulated in some areas of the brain, we hypothesized that patients with chronic visceral (IBS) and somatic (FM) symptoms may be characterized by altered activity in regions where afferent inputs overlap, or where pain-modulating mechanisms are shared. Joint pain *processing* regions include the dorsal horn of the spinal cord (27), thalamic nuclei (and associated primary and secondary somatosensory cortices) (28–30), caudal anterior cingulate cortex (ACC), and anterior insular cortices (29–35). An important pain *modulation* network, which is likely to affect the perception of both visceral and somatic noxious stimuli, involves brainstem structures, such as the periaqueductal gray, the parabrachial nucleus, and the ventromedial medulla (36). This pontine network receives modulatory input from the prefrontal cortex and more rostral aspects of the ACC, and these inputs have been thought to play an important role in mediating emotional and attentional influences on pain perception (37, 38). Based on a meta-analysis of recent human pain imaging studies, Petrovic and Ingvar suggested that the ACC may be divided into three functional subregions: a caudal portion, which is preferentially activated during painful stimuli; an adjacent, and slightly more rostral region (middle ACC), which is activated during attentional tasks; and the most rostral part ("perigenual"), which is activated by emotional tasks and is part of central opioid networks (39,40).

There have been few neuroimaging studies performed in patients with IBS or FM that have employed visceral and somatic pain stimuli. We and others have published studies comparing brain activation responses to rectal distension in IBS patients and healthy controls (25, 31, 32, 41). In most studies, alterations in the activation of ACC subregions were found in the IBS patients compared with the controls. There have been two studies evaluating resting cerebral blood flow in FM patients with single-photon-emission CT (42, 43). Although these studies were done under baseline conditions, and patients with psychological distress symptoms were not excluded, these studies demonstrated only decreased blood flow in subcortical regions (*e.g.*, thalamus, caudate nucleus, and pontine tegmentum) in the FM patients. The presence of comorbid IBS was not assessed in these patients. A more recent study that employed functional magnetic resonance imaging compared brain activations in response to a somatic pain stimulus in 16 FM patients and 16 healthy control subjects (44). The authors found that when a stimulus of identical pressure was applied to the thumbnail, the FM group showed greater activation of the ACC in addition to 12 other regions, compared with the control group.

The goal of the present study was to compare the changes in rCBF produced by a visceral compared with a somatic pressure stimulus in IBS patients with and without FM. We aimed to answer two general questions: 1) Do IBS and IBS + FM patients show altered activation in brain regions receiving viscerosomatic afferent input (somatosensory cortex, caudal ACC, insula, and thalamus)? and 2) Do these two patient groups show altered activation of cortical regions involved in cognitive and emotional pain modulation (prefrontal cortex and more rostral ACC subregions)? Part of these results has been published in abstract form (24).

MATERIALS AND METHODS

Subjects

IBS PATIENTS. Ten female IBS patients (mean age 42 ± 10 yr) were recruited from advertisements and the University of California, Los Angeles (UCLA) Functional Bowel Disease Clinic. Selection criteria included a positive diagnosis by the Rome I criteria (45), a clinical diagnosis of IBS made by a gastroenterologist experienced in the diagnosis of functional bowel disorders, and the exclusion of inflammatory or other structural intestinal disease based on clinical and endoscopic evidence. Four IBS patients were constipation-predominant, one was diarrhea-predominant, and five had alternating bowel habits. None had evidence of FM or other nonvisceral chronic pain conditions.

IBS PATIENTS WITH FM. Ten female patients with IBS + FM (mean age 46 ± 11 yr) were recruited from advertisements and the UCLA Functional Bowel Disease Clinic. All study subjects met selection criteria for IBS (see above). Two of these patients were constipation-predominant, three were diarrhea-predominant, and five had alternating bowel habits (similar to patients with IBS alone). In addition, all subjects were examined for and met the diagnostic criteria for FM according to the 1990 American College of Rheumatology criteria (8) and were previously diagnosed with FM by a rheumatologist.

There were no significant differences in mean age between the patients with IBS alone and coexistent IBS and FM. None of the study subjects were taking medications, including peripherally acting treatments for IBS, centrally acting drugs (anxiolytics, antidepressants, narcotics), or nonsteroidal anti-inflammatory medications for at least 2 wk before the study. All study subjects underwent a pregnancy test before the test, and all tests were negative. Although including patients with FM alone would have been preferable for this study, our experience has been that it is very difficult to recruit this patient group with the following criteria: 1) no centrally acting drugs, 2) no analgesic agents including narcotics, and 3) willingness to undergo the study. Verbal and written consent was obtained from each subject. The VA Greater Los Angeles Healthcare System Research and Development Committee and Committee on Human Studies approved this study.

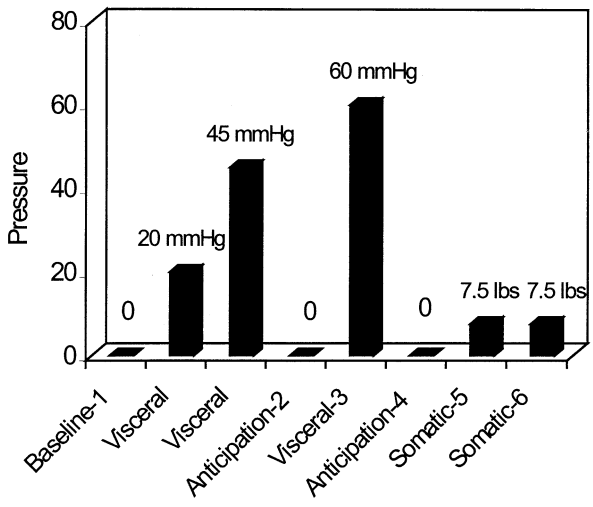

Figure 1. PET protocol. The amount of pressure given during the visceral (rectum, mm Hg) or somatic (arm, lb) conditions is shown on the y axis and numerically above each condition. The scan number is given after the condition label. Note that the 20 mm Hg visceral stimulus condition was not scanned, and there were insufficient number of 45 mm Hg scans to be included in the analysis. The order of the two somatic stimuli was randomized to the active or control tender point on the left arm.

SYMPTOM RATINGS. At the start of the study, IBS patients were asked to rate the intensity and unpleasantness of their abdominal pain for both the past 6 months (chronic) and the past 24 h (acute), using validated verbal descriptor anchored visual analog scales (see description below). The patients with co-existent FM were also asked to rate their somatic pain, using these same scales.

Bowel Symptom Questionnaire

All subjects completed a UCLA bowel symptom questionnaire on encounter with the center. The bowel symptom questionnaire (4) distinguishes abdominal symptoms and bowel habits as well as the presence of extra-intestinal symptoms.

Symptom Checklist 90

All subjects completed the Symptom Checklist 90 (46). This instrument is a reliable and valid measurement of current psychological function, including detection of significant psychological symptomatology. This instrument was used to examine the presence of significant psychological symptoms based on the general symptom index (t score $\geq$ 63).

Somatic and Visceral Pressure Stimuli

The somatic stimulus device consisted of a 7.5-lb weight attached to a syringe plunger with a contact head whose surface area was equal to 1.54 cm^2. This device was used to apply pressure on the two designated somatic points. The mechanical stimulus was applied for 1 min separately to the active (2 cm distal to the left epicondyle) and control somatic point (dorsal distal third of the left forearm). The left epicondyle somatic point is a standard tender point, however several studies have demonstrated decreased pain thresholds both at tender points and at control sites in FM patients (6-12).

Visceral pressure stimulation of the rectum was accomplished using a computer-driven pump (barostat), which allowed for controlled inflations. The rectal balloon catheter consisted of a single latex balloon (external diameter, 5 cm; length of each balloon, 11 cm) attached to a Silastic elastomer tube (external diameter 18 Fr) at both proximal and distal ends (MAK-LA, Los Angeles, CA). Before and after each procedure, each balloon was inflated repeatedly to rule out any leak and to measure intrinsic compliance. The lubricated balloon catheter was inserted into the rectum so that the distal end was 4 cm from the anal orifice. The catheter was secured with tape. The balloon was inflated at a rapid volume rate (870 ml/min) and held at constant pressure plateaus by the barostat for the duration of the trial. A 12-h fast and application of two Fleet enemas (C.B. Fleet, Lynchburg, VA) preceded the rectal balloon placement.

Positron Emission Tomography

The subjects were scanned using a positron emission tomography (PET) scanner, Siemens/CTI 953 tomograph (Siemens-Computer Technology, Knoxville TN), collecting 31 contiguous data planes corresponding to an axial depth of 3.375 mm each, in a 128 $\times$ 128 image matrix. Each subject was positioned in the scanner so that the axis of the scanner was approximately parallel to the glabellar–inion line. An automatic procedure outlined the scalp, and the well-known bulk attenuation coefficient was used to correct the emission scans. rCBF in each subject was measured by recording the distribution of cerebral radioactivity after intravenous bolus infusion of the freely diffusible positron emitting ^{15}O-labeled tracer, $H_2{}^{15}O$. For each measurement, a 120-s scan commenced at the onset of a 25-mCi bolus injection of $H_2{}^{15}O$. Scan onset also coincided with the onset of pressure to the rectal wall or arm, respectively, when the visceral or somatic stimulus conditions were applied. Twelve minutes passed between injections to allow background radiation to decay to less than 10% of the recorded peak. Six rCBF measurements were completed in a single session lasting approximately 2 h.

The PET protocol is shown in Figure 1. Experimental stimulation studies commenced 30 min after balloon placement. Patients closed their eyes during all scans, and extraneous auditory stimuli were excluded by headphones, through which a recorded message provided a general explanation of the distention protocol. A baseline scan was first obtained without balloon inflation. PET scans were attempted during the subsequent visceral and somatic conditions shown in Figure 1. However, an insufficient number of adequate 45-mm Hg PET scans were recorded. Therefore, this condition was excluded from the image analysis. A rectal distension of moderate (45 mm Hg) or intense (60 mm Hg) pressure was delivered by the computerized barostat for 60 s each, with a 12-min interim deflation. During the "no inflation" conditions before and after the 60-mm Hg rectal distension, the subjects were told that they might receive a rectal distension, but none was delivered (anticipation). The

last two PET scans were acquired during the application of the two separate somatic conditions described previously, counterbalanced for order.

Subjective Stimulus Ratings

Subjective sensory intensity and unpleasantness of each visceral and somatic stimulus was assessed with similar descriptor anchored visual analog scales as described for symptom assessment (47). The sensory intensity scale consisted of descriptors of increasing intensity, ranging from "no sensation" to "extremely intense," arrayed along a 20 cm vertical bar. The unpleasantness scale consisted of descriptors of increasing unpleasantness, ranging from "neutral" to "very intolerable." Ratings were assessed after each stimulus. Each stimulus was also rated on a 10-cm visual analog scale of anxiety (anchored by "no anxiety" and "greatest anxiety imaginable").

Statistical Analysis

SUBJECTIVE SYMPTOMS. The following were compared between the IBS and IBS + FM groups: acute and chronic ratings of the intensity and unpleasantness of current abdominal pain and discomfort, subjective response to the visceral and somatic stimuli during the PET scanning sessions, and Symptom Checklist 90 psychological general symptom scores. In addition, acute and chronic ratings of abdominal compared with somatic pain were compared in the IBS + FM group. These comparisons were made using Student *t* test. Perceptual ratings of the 60-mm Hg visceral stimulus and the somatic stimulus (average ratings of the two somatic stimuli) were compared for each group using a *t* test. Statistical significance was assessed at the $p < 0.05$ level. All analyses were conducted with the SPSS statistical software package (SPSS, Chicago, IL.).

IMAGE DATA ANALYSIS. The following procedures were carried out using SPM99 (Wellcome Trust Center (London, UK) for the Study of Cognitive Neurology), described in detail elsewhere (48, 49). All scans within each individual subject were corrected for head movement by alignment with the first scan. Each realigned set of scans was then registered into the standardized anatomic space of the average magnetic resonance image provided by the Montreal Neurological Institute. To increase the signal-to-noise ratio and accommodate variability in functional anatomy, each image was smoothed in x, y, and z dimensions with a Gaussian filter of 12 mm (full width half maximum).

At each voxel, a standard parametric statistical model used multiple linear regression to partition variability in blood flow, measured as normalized radioactive counts, in terms of experimental effects, confounds, and residual variance. Subject main effects were defined as confounds, with global activity removed by proportional scaling. Linear effects of scan order were removed as confounds through use of subject-specific covariates. Voxel-by-voxel one-tailed *t* tests then assessed the effects of visceral and somatic pressure and displayed them as statistical parametric maps.

The object of these studies was to compare brain activation (rCBF) between IBS and IBS + FM patients in response to rectal compared with somatic pressure. Preliminary investigations did not detect significant differences between individual visceral pressures, individual somatic pressures, or between the three different scans in which no pressure was applied. However, it is possible that with greater statistical power, differences between these conditions could have been demonstrated. Alternatively, the lack of detectable differences to individual visceral or somatic stimuli may be due to a greater variability of brain responses to fixed pressure stimuli as compared to using individualized pressure levels equated for subjective sensory ratings. Because we were primarily interested in the unique effects of visceral and somatic pressure stimuli, we maximized statistical power by contrasting scans recorded during each type of pressure with all of the scans not featuring this type of pressure. Therefore, the brain response to the somatic stimuli was assessed by contrasting scans 5-6 with scans 1-4 (Figure 1). Likewise, the response to visceral stimulus was assessed by contrasting scan 3 with scans 1, 2, 4, 5, and 6. Therefore, these comparisons were insensitive to rCBF changes that occurred during both visceral and somatic pressure.

Differences between IBS and IBS + FM patients were assessed as group × condition interactions. The effects of visceral and somatic pressure were separately analyzed in the two groups of IBS patients and used to mask the interaction contrast to rule out effects due solely to deactivations. That is, to ensure proper interpretation, interactions were masked at the $p < 0.01$ height level by the relevant activation in the patient group where that activation was being interpreted. In other words, any reported activation represents significantly increased activation in the designated patient group (and not solely a deactivation of the other group) and a significant difference between the two groups.

For statistical parametric map display purposes, any cluster larger than 23 voxels (extent threshold = 0.05) with a signal intensity corresponding to a threshold of $p < 0.01$ is depicted. This follows other work with functional imaging and pain or visceral distension (25, 50, 51) and reduces the possibility of false-negative reporting (52). However, to reduce the risk of over-interpreting false-positive findings, clusters are tabled only if they were significantly activated after correction for total brain volume, or if there is a clear *a priori* reason to expect activation. Because this study seeks to analyze differences between two clinical subgroups, the brain activation responses to the somatic and visceral stimuli are presented using between-group differences and are shown in the figures to demonstrate the significant areas of activation in the medial structures.

Determination of the subregion of the ACC that was significantly activated was made by superimposing the coordinates of the region onto the schematic of the three subregions of the ACC as illustrated in a recent review by Petrovic and Ingvar (37).

Table 1. Clinical Symptom Ratings in the IBS and IBS + FM Patients

Symptom Rating	IBS Patients (n = 10)	IBS + FM Patients (n = 10)
Abdominal pain		
Acute sensory intensity	10.5 ± 1.8 cm	7.1 ± 1.7 cm
Acute unpleasantness	8.7 ± 1.9 cm	6.5 ± 1.5 cm
Chronic sensory intensity	15.4 ± 0.8 cm	11.3 ± 1.6 cm*
Chronic unpleasantness	14.2 ± 0.8 cm	10.3 ± 1.2 cm*
Muscle pain		
Acute sensory intensity		10.0 ± 1.5 cm
Acute unpleasantness		7.8 ± 1.3 cm
Chronic sensory intensity		13.5 ± 1.1 cm†
Chronic unpleasantness		12.0 ± 1.2 cm

* $p < 0.05$ compared with IBS patients.
† $p < 0.05$ compared with chronic intensity rating of abdominal pain in IBS + FM patients.

RESULTS

Subjective Symptom Ratings

Subjective ratings of acute and chronic abdominal pain were higher in the IBS patients compared with the IBS + FM patients for both intensity and unpleasantness ($p < 0.05$ for chronic [6-month] ratings; Table 1). Comparing the symptom ratings of somatic pain with those of abdominal pain in the IBS + FM patients, chronic somatic pain was rated as more intense than chronic abdominal pain ($p < 0.02$). These ratings suggest that IBS + FM patients perceive their abdominal pain to be less intense than their somatic pain, and less intense than that perceived by patients with IBS alone. With regard to psychological symptom scores, only one IBS patient and two IBS + FM patients had elevated general symptom index scores (p = ns).

Differences in Brain Activation Between IBS and IBS + FM Patients

IBS GROUP: GREATER ACTIVATION OF THE MIDDLE ACC TO NOXIOUS VISCERAL DISTENSION. The interaction of condition with presence or absence of FM within IBS patients showed rCBF changes only in the middle subregion of the ACC, as depicted in Figure 2. The largest site activated more in response to visceral distension in the IBS group compared with the IBS + FM group consisted of 76 voxels in the middle ACC (peak voxel 10, 14, 38; $t = 2.89$; uncorrected $p = 0.003$). In response to the visceral stimulus, there were no areas more activated in the IBS + FM group compared with the IBS group.

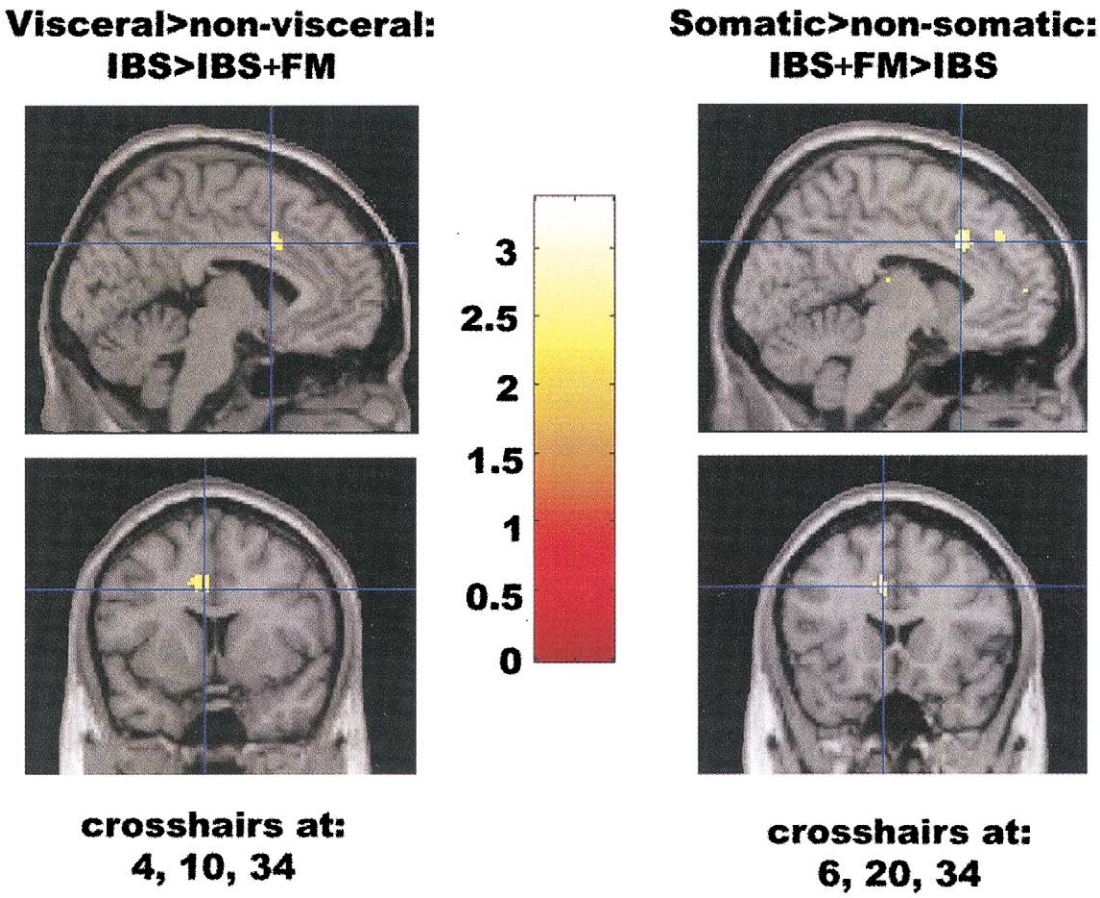

Figure 2. Results for the interaction of type of stimulus (visceral, somatic), and clinical group (IBS and IBS + FM). There was greater activation of the middle ACC in IBS patients in response to visceral distension and in the IBS + FM patients in response to somatic pressure stimuli.

IBS + FM GROUP: GREATER ACTIVATION OF THE MIDDLE ACC TO SOMATIC PRESSURE. In response to the somatic stimulus, there were no areas more activated in the IBS group compared with the IBS + FM group. However, 217 voxels in the middle ACC showed a greater activation in response to somatic pressure in the IBS + FM group than in the IBS group (peak voxel 12, 42, 36; $t = 3.35$; uncorrected $p = 0.001$), as shown in Figure 2. All of these voxels were also activated at the $p < 0.01$ level in the IBS + FM group considered alone. We also measured rCBF in response to the somatic stimuli compared with the other conditions *excluding* those with visceral distension (baseline and two no inflation conditions), and there was greater activation of the middle ACC extending to the perigenual ACC (uncorrected $p < 0.001$). The thalamus was also activated (uncorrected $p < 0.05$).

Subjective Stimulus Ratings During Viscerosomatic Stimulation

Both sensory intensity (16.1 ± 0.8 *vs* 16.1 ± 0.7) and unpleasantness (14.5 ± 1.1 *vs* 13.3 ± 1.1) ratings in response to the 60-mm Hg rectal distension were similar in the IBS and IBS + FM groups, respectively. The visceral stimulus was rated as "very intense" and "intolerable." With regard to the somatic stimulus, the IBS + FM patients rated the somatic stimuli similarly when compared with IBS patients without FM for both intensity (13.2 ± 1.0 *vs* 10.1 ± 1.6, $p = 0.13$) and unpleasantness (11.0 ± 0.8 *vs* 8.7 ± 1.3, $p = 0.15$) comparing the subjective ratings to the active vs. control somatic points, the IBS + FM patients rated the intensity (13.5 ± 0.7 vs. 12.9 ± 1.6) and unpleasantness (11.8 ± 0.7 vs. 10.3 ± 1.4) of the active and control somatic points similarly. However, the IBS patients rated the active tender point as more unpleasant (9.5 ± 1.2 vs. 8.0 ± 1.5, $p < 0.05$) but of similar intensity (10.1 ± 1.6 vs. 10.2 ± 1.8) compared to the control point. The intensity ratings of the visceral stimulus were significantly higher than the intensity ratings of the somatic stimuli in both groups ($p < 0.05$). However, the unpleasantness ratings of the visceral stimulus were only higher than those of the somatic stimulus in the IBS group. IBS + FM patients reported equivalent unpleasantness in response to the visceral and somatic stimuli. Anxiety ratings to the visceral and somatic stimuli were not different between the two groups.

DISCUSSION

This study considered the hypothesis that the high frequency of symptom overlap between patients with IBS and FM may be due in part to altered functions in brain regions involved in processing and/or modulation of both visceral and somatic afferent inputs. We used potentially noxious mechanical stimuli delivered either to the left forearm or to the rectal wall to produce somatic and visceral pain, respectively. Both IBS groups rated the visceral and somatic stimuli similarly. However, whereas the visceral stimulus produced greater unpleasantness than did the somatic stimulus in the IBS group, there was no difference in unpleasantness elicited by the two types of stimuli in the IBS + FM group.

Patients with IBS (and greater GI pain symptom severity than IBS + FM) had greater activation of the ACC in response to visceral distension than did patients with IBS + FM. This is consistent with our finding that IBS patients had significantly higher ratings of abdominal pain over the past 6 months compared with the IBS + FM patients. In contrast, patients with IBS + FM (and greater somatic pain symptom severity) had greater activation of the same brain region in response to somatic stimuli than did patients with IBS. This is consistent with the presence of chronic somatic pain and the fact that the somatic stimuli produced as much unpleasantness as the visceral stimulus in the IBS + FM patients. Thus, enhanced activation of the ACC by viscerosomatic afferent input may play a role in the pathophysiology of altered perception of visceral and somatic pain in both syndromes.

Greater activation of the ACC was seen in response to the visceral stimulus in the IBS compared with the IBS + FM group and in response to somatic stimuli in the IBS + FM group compared with the IBS group. Although the somatic stimulus was always presented after the visceral stimuli, an order effect is unlikely to account for the finding of greater middle ACC activation in both the IBS patients to visceral pain and the IBS + FM patients to somatic pain. Thus, enhanced ACC activation occurs in both patient groups but is associated with different classes of sensory stimuli.

Concepts regarding the specific role of the ACC in pain perception have evolved from neuroanatomic studies in animals to the observations derived from functional brain imaging studies in humans (53). Considerable functional and neuroanatomic evidence supports the concept that the ACC has functionally distinct subregions. Based on a meta-analysis of human studies using cognitive and emotional stimuli, Bush et al. proposed a subdivision into the ventral subregions (infralimbic, perigenual) primarily concerned with regulation of emotion, and the dorsal subregions concerned with cognitive functions, such as attentional demand and response selection (40, 54). Based on a meta-analysis of human pain studies, Petrovic and Ingvar (37) recently proposed a similar subdivision into a more caudal portion of ACC, which is consistently activated by stimulation of somatic and visceral nociceptive afferents (31, 32, 35, 52). Immediately rostral to this area is a middle ACC subregion concerned with attentional processes, and the most rostral ACC subregion (also referred to as perigenual ACC) is concerned with emotional processes (37, 38). Increases in cerebral blood flow in the middle ACC correlate with somatic pain ratings of unpleasantness (55, 56) and intensity (56) during hypnotic suggestion. Considerable evidence suggests that this brain region is not simply involved in the processing of afferent information associated with negative emotion (57, 58). Rather, subregions of the ACC seem to play a prominent role in regulation of attention to afferent information of both negative and positive valence, and the

subregions organize the most appropriate behavioral response to sensory stimuli while taking into account its affective component (56). One plausible explanation for the greater activation of the middle ACC subregion in IBS patients to a rectal distension and in IBS + FM patients to somatic pressure is that these findings may represent greater attentional attribution and therefore increased conscious processing of visceral and somatic stimuli in the two patient groups, respectively. The fact that no significant group differences in rCBF were observed in other areas receiving viscerosomatic input and known to be involved in the processing of painful stimuli, such as insula, thalamus, or somatosensory cortex, makes it highly unlikely that the differences in subjective symptom reports, as well as in ACC activation, are related primarily to differences in afferent input from sensitized visceral *versus* somatic afferent pathways. This explanation is supported by Whitehead *et al.* in their extensive review of the comorbidity of IBS with other disorders, including FM (1). These authors suggest that, although these disorders may be manifestations of interacting physiologic and cognitive factors, they may be distinct disorders and that their strong co-morbidity suggests a common feature, which is most likely psychological.

Numerous functional imaging studies provide a platform for informed speculation as to the role of ACC in the pathophysiology of IBS, FM, and their extensive co-morbidity. This region has been consistently activated in patients with IBS or FM compared with controls. Two studies comparing IBS patients with healthy control subjects demonstrated greater activation of the middle ACC (but not thalamus and insula) by a rectal pressure stimulus (31, 32). Interestingly, the same subregion of the ACC was activated to a greater degree in FM patients compared with healthy controls during a somatic pressure stimulus (44). The authors of the latter study concluded that their findings suggested that FM is characterized by central augmentation of pain processing (44). Thus, the main differences between patients with IBS or FM and healthy individuals, as well as between the IBS subgroups, involves the attentional processing of stimuli that are assessed as clinically relevant, rather than differences in increased afferent input of noxious visceral or somatic stimuli. This interpretation is consistent with the hypothesis proposed by Whitehead et al. (1) for IBS patients (*i.e.*, that cognitive traits, such as selective attention, may be important in the altered perception of visceral stimuli by these patients). In patients with chronic pain disorders, such as IBS and/or FM, greater activation of the ACC may initially occur in response to a potentially threatening stimulus but subsequently become chronically activated owing to enhanced attentional processing. This could lead to hypervigilance that might generalize to similar stimuli not necessarily associated with the disease symptoms.

In summary, greater activation of the middle subregion of the ACC in patients with IBS without FM in response to visceral stimuli and in IBS + FM patients in response to somatic stimuli suggests an alteration of normal attentional attribution to specific afferent information from different body regions. Future studies using the rapidly advancing functional neuroimaging techniques will help increase our understanding of the central processing and modulation of visceral and somatic sensory information and how alterations in these processes might manifest as syndromes characterized by chronic visceral and/or somatic discomfort and pain, such as IBS and FM.

Reprint requests and correspondence: Lin Chang, M.D., UCLA/CURE Clinical Research Center, West LA VA Medical Center, C.N.S. Center for Neurovisceral Sciences & Women's Heath, Building 115, Room 223, 11301 Wilshire Boulevard, Los Angeles, CA 90073.

Received Aug. 19, 2002; accepted Dec. 30, 2002.

REFERENCES

1. Whitehead WE, Palsson O, Jones KR. Systemic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? Gastroenterology 2002; 122:1140–56.
2. Veale D, Kavanagh G, Fielding JF, et al. Primary fibromyalgia and the irritable bowel syndrome: Different expressions of a common pathogenetic process. Br J Rheumatol 1991;30: 220–2.
3. Mertz H, Naliboff B, Munakata J, et al. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40–52.
4. Munakata J, Naliboff B, Harraf F, et al. Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. Gastroenterology 1997;112:55–63.
5. Naliboff BD, Munakata J, Fullerton S, et al. Evidence for two distinct perceptual alterations in irritable bowel syndrome. Gut 1997;41:505–12.
6. Scudds RA, Rollman GB, Harth M, et al. Pain perception and personality measures as discriminators in the classification of fibrositis. J Rheumatol 1987;14:563–9.
7. Tunks E, Crook J, Norman G, et al. Tender points in fibromyalgia. Pain 1988;34:11–9.
8. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology criteria for the classification of fibromyalgia: A report of the Multicenter Criteria Committee. Arthritis Rheum 1990;1990:33:160–72.
9. Granges G, Littlejohn G. Pressure pain threshold pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome. Arthritis Rheum 1993;36:642–6.
10. Gibson SJ, Littlejohn GO, Gorman MM, et al. Altered heat pain thresholds and cerebral event-related potentials following painful CO_2 laser stimulation in subjects with fibromyalgia syndrome. Pain 1994;58:185–93.
11. Lautenbacher S, Rollman GB, McCain GA. Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain 1994;59:45–53.
12. McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: Evidence of perceptual amplification. Pain 1996;66:133–44.
13. Ford MJ, Miller PM, Eastwood J, et al. Life events, psychiatric illness and the irritable bowel syndrome. Gut 1987;28:160–5.
14. Goldenberg DL. Psychiatric and psychologic aspects of fibromyalgia syndrome. Rheum Dis Clin North Am 1989;15:105–14.
15. Drossman DA, Thompson WG. The irritable bowel syndrome: Review and a graduated multicomponent treatment approach. Ann Intern Med 1992;116:1009–16.

16. Haanen HC, Hoenderdos HT, van Romunde LK, et al. Controlled trial of hypnotherapy in the treatment of refractory fibromyalgia. J Rheumatol 1991;18:72–5.
17. White KP, Nielson WR. Cognitive behavioral treatment of fibromyalgia syndrome: A follow-up assessment. J Rheumatol 1995;22:717–21.
18. Gruber AJ, Hudson JI, Pope HGJ. The management of treatment-resistant depression in disorders on the interface of psychiatry and medicine. Fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder. Psychiatr Clin North Am 1996;19:351–69.
19. Goodnick PJ, Sandoval R. Psychotropic treatment of chronic fatigue syndrome and related disorders. J Clin Psychiatry 1993;54:13–20.
20. Whitehead WE, Bosmajian L, Zonderman AB, et al. Symptoms of psychological distress associated with irritable bowel syndrome. Gastroenterology 1988;95:709–14.
21. Mertz H, Fass R, Hirsh T, et al. Amitryptiline for functional dyspepsia: Affect on symptoms, gastric sensitivity and sleep. Gastroenterology 1995;108:A649 (abstract).
22. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: A technical review for practice guideline development. Gastroenterology 1997;112:2120–37.
23. Clouse RE. Antidepressants for functional gastrointestinal syndromes. Dig Dis Sci 1994;39:2352–63.
24. Chang L, Mayer EA, Munakata J, et al. Differences in left prefrontal activation to visceral and somatic stimuli assessed by O^{15}-water PET in female patients with irritable bowel syndrome (IBS) and fibromyalgia. Gastroenterology 1998; 114:A732 (abstract).
25. Silverman DH, Munakata JA, Ennes H, et al. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 1997;112:64–72.
26. Naliboff B, Silverman DHS, Munakata J, et al. Altered regional brain activity to rectal distension following repetitive sigmoid stimulation in IBS. Gastroenterology 1998;114:A809.
27. Al-Chaer ED, Feng Y, Willis WD. Comparative study of viscerosomatic input onto postsynaptic dorsal column and spinothalamic tract neurons in the primate. J Neurophysiol 1999;82:1876–82.
28. Schnitzler A, Volkmann J, Enck P, et al. Different cortical organization of visceral and somatic sensation in humans. J Neurosci 1999;11:305–15.
29. Coghill RC, Talbot JD, Evans AC, et al. Distributed processing of pain and vibration by the human brain. J Neurosci 1994;14:4095–108.
30. Casey KL. Forebrain mechanisms of nociception and pain: Analysis through imaging. Proc Natl Acad Sci U S A 1999; 96:7668–74.
31. Naliboff BD, Derbyshire SWG, Munakata J, et al. Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365–75.
32. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distension. Gastroenterology 2000;118:842–8.
33. Derbyshire SW. Exploring the pain "neuromatrix." Curr Rev Pain 2000;4:467–77.
34. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000;30:1752–61.
35. Aziz Q, Thompson DG, Ng VWK, et al. Cortical processing of human somatic and visceral sensation. J Neurosci 2000;20: 2657–63.
36. Fields HL, Basbaum AI. Endogenous pain control mechanisms. In: Wall PD, Melzack R, eds. Textbook of pain. New York: Churchill Livingstone, 1989:206–19.
37. Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. Pain 2002;95:1–5.
38. Villemure C, Bushnell MC. Cognitive modulation of pain: How do attention and emotion influence pain processing? Pain 2002;95:195–9.
39. Petrovic P, Kalso E, Petersson KM, et al. Placebo and opioid analgesia–imaging a shared neuronal network. Science 2002; 295:1737–40.
40. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215–22.
41. Bernstein CN, Frankenstein UN, Rawsthorne P, et al. Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. Am J Gastroenterol 2002;97:319–27.
42. Kwiatek R, Barnden L, Tedman R, et al. Regional cerebral blood flow in fibromyalgia: Single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthritis Rheum 2000;43:2823–33.
43. Mountz JM, Bradley LA, Modell JG, et al. Fibromyalgia in women. Arthritis Rheum 1995;38:926–38.
44. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.
45. Drossman DA, Thompson GW, Talley NJ, et al. Identification of subgroups of functional gastrointestinal disorders. Gastroenterol Int 1990;3:159–72.
46. Derogatis LR. SCL-90R. Administration, scoring and procedures manual–II. Towson, MD: NCS, 1983.
47. Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. Pain 1978;5:5–18.
48. Friston KJ, Holmes AP, Worsley KJ, et al. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 1995;2:189–210.
49. Friston KJ, Price CJ, Fletcher P, et al. The trouble with cognitive subtraction. Neuroimage 1996;4:97–104.
50. Derbyshire SW, Jones AK, Gyulai F, et al. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 1997;73:431–45.
51. Hsieh JC, Belfrage M, Stone-Elander S, et al. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 1995;63:225–36.
52. Derbyshire SWG. Meta-analysis of thirty-four independent samples studied using PET reveals a significantly attenuated central response to noxious stimulation in clinical pain patients. Curr Rev Pain 1999;3:265–80.
53. Vogt BA, Vogt LJ, Nimchinsky EA, et al. Primate cingulate cortex chemoarchitecture and its disruption in Alzheimer's disease. In: Bloom FE, Bjorklund A, Hokfelt T, eds. Handbook of chemical neuroanatomy. New York: Elsevier, 1997:455–528.
54. Drevets WC, Raichle ME. Suppression of regional cerebral blood during emotional versus higher cognitive implications for interactions between emotion and cognition. Cogn Emotion 1998;12:353–85.
55. Rainville P, Duncan GH, Price DD, et al. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997;277:968–71.
56. Faymonville ME, Laureys S, Degueldre C, et al. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology 2000;92:1257–67.
57. Damasio AR, Grabowski TJ, Bechara A, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000;3:1049–56.
58. Bartels A, Zeki S. The neural basis of romantic love. Neuroreport 2000;11:3829–34.