Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study

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ABSTRACT

Objective To address the role of anxiety and depression symptoms in altered pain processing in irritable bowel syndrome (IBS).

Design In this functional magnetic resonance imaging study, the blood oxygen level-dependent (BOLD) response to rectal distensions delivered at previously determined individual discomfort thresholds was assessed.

Patients 15 female patients with irritable bowel syndrome (IBS) and with normal rectal pain thresholds, and 12 healthy women.

Measures The correlation of anxiety and depression symptoms, measured with the Hospital Anxiety and Depression Scale (HADS), with subjective pain ratings and the BOLD response during distension-induced brain activation were analysed within IBS. Group differences in pain-induced brain activation with and without controlling for HADS scores were evaluated.

Results Patients with IBS experienced significantly more pain and discomfort upon rectal distensions in the scanner, despite unaltered rectal sensory thresholds. Anxiety and depression scores were associated with these subjective stimulus ratings, but not with rectal sensory thresholds. Anxiety symptoms in IBS were significantly associated with pain-induced activation of the anterior midcingulate cortex and pregenual anterior cingulate cortex. Depression scores correlated with activation of the prefrontal cortex (PFC) and cerebellar areas within IBS. Group comparisons with the two-sample t test revealed significant activation in the IBS versus controls contrast in the anterior insular cortex and PFC. Inclusion of anxiety and depression scores, respectively, as confounding variables led to a loss of significant group differences.

Conclusions Altered central processing of visceral stimuli in IBS is at least in part mediated by symptoms of anxiety and depression, which may modulate the affective—motivational aspects of the pain response.

INTRODUCTION

The aetiology and pathophysiology of visceral hyperalgesia in irritable bowel syndrome (IBS) may involve peripheral, spinal and central pathways but remains incompletely understood.[1] The relevance of centrally mediated, psychological mechanisms is supported by evidence that increased sensitivity to visceral stimuli is explained by an increased tendency to report pain, rather than enhanced neuro-sensory sensitivity.[2] Further support comes from studies documenting that negative emotions induced by psychological stress,[3 4] pharmacological manipulation of stress mediators,[5] or hypnosis[6] affect rectal pain sensitivity in IBS. At the same time, IBS patients display enhanced negative emotional responses to various stressful situations[4 7] and are characterised by a wide range of affective disturbances, including symptoms of depression and anxiety.[8] Whether and to what extent affective disturbances contribute to disturbed neural responses to visceral stimuli in IBS remains unclear.

Interactions between affective and cognitive processes and the brain response to pain are increasingly appreciated in the context of somatic pain,[9–12] but imaging studies addressing affective modulation in visceral pain models remain sparse.[13–15] Therefore, we aimed to test the hypotheses that affective disturbances [1] are associated with the subjective response to painful visceral stimuli within IBS,[2] correlate with brain activation during painful rectal distensions, and[3] account for at least some of the group differences in pain-induced brain activation when compared to healthy controls. Given that symptoms of anxiety and depression constitute common psychological co-morbidities in IBS,[8] we chose to use scores of the Hospital Anxiety and Depression Scale (HADS) as correlates in the analyses.

MATERIALS AND METHODS

Recruitment, and inclusion and exclusion criteria

Patients with IBS who met the Rome III criteria for IBS and had an established diagnosis for more than 1 year were recruited from two outpatient clinics and one gastroenterology practice in Essen, Germany. Healthy female controls were recruited through public advertisement in the surrounding community. A screening process was accomplished which included a personal interview, completion of questionnaires, and standard physical examination with a manual rectal examination. General exclusion criteria included age <18 years and >45 years, body mass index ≥30, any concurrent medical condition, including neurological, cardiovascular, immunological or endocrine conditions. Any history of gastrointestinal conditions (other than IBS for the IBS group) or anal/rectal tissue damage was exclusionary. All women were evaluated digitally for internal anal tissue damage (eg, painful haemorrhoids) which may interfere with balloon placement. For the IBS group, a history of psychological conditions or presently increased scores on the HADS[16] was not exclusionary;

however, current use of psychiatric medications led to exclusion to avoid confounding of the results. For healthy women, any evidence of previous or current psychiatric conditions, including HADS scores ≥11 (ie, the cut-off for clinically relevant symptoms), was exclusionary. Right-handedness was ensured using a validated questionnaire.[17] A structural magnetic resonance imaging (MRI) scan was completed to exclude any brain tissue abnormality. Pregnancy was excluded with a commercially available urinary test carried out on the day of the functional MRI (fMRI) study. All participants gave written informed consent prior to participation, and were paid for their participation.

Study design

The study was comprised of two study days which took place no more than 7 days apart. On the first study day, rectal perceptual and pain thresholds were determined using a pressure-controlled barostat device. In addition, a structural MRI scan was completed to exclude structural abnormality and to familiarise participants with the MRI. On the second study day, rectal distension-induced brain activation was measured with fMRI using distension pressures at the individual discomfort level as determined on the first study day. This was done to establish similar perceptual intensities between groups.

Rectal distensions

Rectal distensions were carried out with a pressure-controlled barostat system (modified ISOBAR 3 device; G & J Electronics, Toronto, Ontario, Canada) as previously described.[18 19] Briefly, an infinitely compliant catheter-affixed polyethylene bag of cylindrical shape with a diameter of 10 cm and a maximal volume of 600 ml when fully inflated was attached to a rectal tube with an outer diameter of 5 mm. The balloon was inserted into the rectum after lubrication, with the distal bag margin 5 cm beyond the anal verge. Rectal perception and pain thresholds were determined using staircase distensions with random pressure increments of 2–10 mm Hg. Each pressure was maintained for 10 s, then subjects were prompted with a light signal to rate the sensation by using a rating scale, ie, 1= no perception, 2= doubtful perception, 3= sure perception, 4= no or very little discomfort, 5= discomfort, 6= pain). Between distensions, pauses with complete balloon deflation lasting approximately 10 s were accomplished. For ethical reasons, the maximal distension pressure was set at 50 mm Hg, and inflation was discontinued whenever a subject rated the distension as painful. The threshold for first perception was defined as the distending pressure when the subjects rating changed from a rating of 2 ('doubtful perception') to 3 ('sure perception'), and the pain threshold was defined as the pressure at which subjects indicated 6 ('pain'). For ethical reasons, the pressure corresponding to a rating of 6 ('pain') was not utilised for repeated distensions in the scanner. Instead, we chose the pressure corresponding to a rating of 5 ('discomfort').

Questionnaires

Frequency and severity of a variety of gastrointestinal symptoms as well as of typical extra-intestinal symptoms of IBS were assessed with a standardised questionnaire. Symptoms of anxiety and depression were assessed with the German HADS which provides cut-offs for mild to moderate depressive and anxiety symptoms, respectively (ie, scores ≥8–10 indicate mild to moderate symptoms; scores ≥11 indicate clinically relevant symptoms).[16] Although the HADS assesses symptoms over the past week, scores are demonstrably highly reliable and correlate with repeated assessments over weeks and even months.[16] For additional psychological characterisation of participants, emotional distress was measured with the German version of the SCL-90-R.[20] The German state version of the State–Trait–Anxiety Index (STAI-S) was used to assess acute anxiety prior to and after scanning in order to document possible group differences in present state negative emotions which may also influence the neural response to pain.[21] Visual analogue scales (VAS) scales were completed after scanning to quantify how painful subjects rated the distensions delivered during scanning, how much urge to defecate they had felt during distensions, and how much overall discomfort they had experienced.

fMRI: imaging and analyses

All MR images were acquired using a 1.5 T MR (Sonata; Siemens, Erlangen, Germany) with a standard head coil. A three-dimensional fast low angle shot (FLASH) sequence (repetition time (TR), 10 ms; time to echo (TE), 4.5 ms; flip angle 30°, field of view (FOV), 240 mm; matrix, 512; slice thickness, 1.5 mm) was acquired for individual co-registration of functional and structural images. Blood oxygen level-dependent (BOLD) contrast images were acquired using an echo–planar technique (TR, 3100 ms; TE, 50 ms; flip angle, 90°; FOV, 240 mm; and matrix 64) with 34 transversal slices angulated in direction of the corpus callosum with a thickness of 3 mm and a 0.3 mm slice gap. For the fMRI study, a block design was implemented in which phases of distension alternated with phases without distension, as previously described.[19] Ten scans formed a phase both during active as well as passive phases, each lasting 31 s. However, the onsets of the active conditions was delayed by two scans since the first 6 s were needed to inflate the balloon. This resulted in an active phase of 25 s. A total of 12 rectal distensions were applied, comprised of six non-painful distensions (data not shown) followed by six painful distensions.

For data analysis, SPM 05 software (Wellcome Department of Cognitive Neurology, London, UK) was used. Prior to statistical analysis, images were realigned using sinc interpolation and normalised to the standard stereotactic space corresponding to the template from the Montreal Neurological Institute (MNI; http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Bilinear interpolation was applied for normalisation. The images were smoothed with an isotropic Gaussian kernel of 9 mm. A voxel-by-voxel comparison according to the general linear model was used to calculate differences of activation between active and resting phases. The model consisted of a box-car function convolved with the haemodynamic response function (hrf) and the corresponding temporal derivative. High-pass filtering with a cut-off frequency of 120 s and low-pass filtering with the hrf was applied. Single-subject contrast images were entered into random effects group analyses with the subjects being the random factor. We performed one-sample and two-sample t tests, and regression analyses. In a whole-brain analysis, significant signal changes for each contrast were assessed by means of a t statistic on a voxel-by-voxel basis.[22] The resulting set of voxel values for each contrast constituted a statistical parametric map (SPM) of the t statistic. One-sample t tests (OSTs) were computed for each group, and a two-sample t test was computed for comparison between the patients with IBS and the control group. Two random-effects analyses were performed using HADS anxiety and depression scores, respectively, as confounding variables. In these analyses, we used an initial height threshold of $p<0.001$ (uncorrected) and subsequent small-volume correction (SVC using family-wise error correction (FWE)) in a priori regions of interest (ROIs) at a level of $p<0.05$.

These regions were pre-defined based on previous imaging findings on visceral pain processing in IBS and healthy subjects[19 23 24] and comprised the insular cortex (IC), prefrontal cortex (PFC), amygdala (AMY), somatosensory cortices, periaqueductal grey (PAG), thalamus (THA), and subregions of the cingulate cortex which were determined based on the paper by Vogt.[25] Correction was based on peak coordinates (ignoring laterality) obtained from earlier studies, and specifically the amygdala[26] and the PAG[19] were corrected using spheres of 6 mm radius, whereas the thalamus,[27] anterior cingulate, midcingulate and posterior cingulate regions[28] were corrected using spheres of 8 mm radius, and the primary and secondary somatosensory cortices,[19] insula[27] and PFC[29] were corrected using spheres of 12 mm radius (see table 3).

In multiple regression analyses, fMRI data from patients with IBS were correlated with HADS scores with differential activity (distension > baseline) as the dependent variable. This was done only for the IBS group, since a priori the control group was recruited to have no psychological disturbances. No a priori ROIs were defined for multiple regression analyses since these were exploratory and, for analysis, we performed whole-brain statistics at p uncorrected <0.001, and report additionally results following FWE correction (p<0.05). All SPM MNI coordinates were converted to Talairach space for presentation of the results.

Statistical analyses of non-fMRI data

For non-fMRT data, Kolmogorov–Smirnov tests were used to establish normal distribution. Comparisons of the groups with regard to sociodemographic and psychological variables were then accomplished using independent-samples t tests or χ^2 tests for dichotomous variables. Correlations were calculated by computing Pearson's r. The alpha level for significance was set at 0.05. All non-fMRI data are shown as mean ± standard error of the mean (SEM).

RESULTS

Participants

Fifteen female patients with IBS and 12 healthy female controls participated. In no case was there any evidence of brain tissue abnormality on structural MRI. Patients with IBS did not differ in sociodemographic parameters from controls, with the exception of age, and expectedly demonstrated higher scores on psychological scales (table 1). Two patients had a prior diagnosis of depression. Based on the HADS, one patient currently showed clinically relevant symptoms of depression and two patients had clinically relevant anxiety scores. Several patients demonstrated HADS scores in the mild to moderate range (table 1). Regarding symptom history in IBS, symptom duration was over 10 years in 40% (N=6), and between 2 and 5 years in 53.3% (N=8) of patients. Forty per cent (N=6) experienced IBS symptoms daily, and 26.7% (N=4) more than twice per week. Fifty-three per cent (N=8) reported that IBS interfered much or very much with daily life. Forty per cent (N=6) were classified as diarrhoea-predominant, 13.3% (N=2) as constipation-predominant, and 40% (N=6) had alternating symptoms of diarrhoea and constipation.

Assessment of rectal thresholds on the first study day (prior to the fMRI study) revealed comparable thresholds for first perception (17.9±1.5 mm Hg for IBS, 17.6±1.1 mm Hg for controls) as well as for pain (35±2.3 mm Hg for IBS, 32.8±2.0 mm Hg for controls). As a result, the distension pressures used in the following fMRI study on study day 2 did not differ between groups as these were based on individual pain thresholds.

Table 1 Sociodemographic and psychological characteristics

Characteristic	IBS (N=15)	Controls (N=12)	p Value*
Age, years	42.4 (2.9)	31.4 (2.3)	p<0.05
Weight, kg	65.1 (3.1)	63.4 (4.0)	NS
Married, % (N)	46.7 (7)	50 (6)	NS
Education >12 years, % (N)	40.0 (6)	66.7 (8)	NS
Employment, full or part time, % (N)	66.7 (10)	75 (9)	NS
HADS depression score	3.9 (1.0)	1.7 (0.4)	NS
HADS anxiety score	7.4 (1.0)	4.6 (0.7)	p<0.05
HADS depression scores ≥8, % (N)	20.0 (3)	0 (0)	NS
HADS anxiety scores ≥8, % (N)	40.0 (6)	8.3 (1)	p=0.07
SCL-90-R somatisation	51.9 (2.5)	48.4 (2.5)	NS
SCL-90-R obsessive–compulsive	55.1 (2.4)	48.0 (2.3)	p<0.05
SCL-90-R interpersonal sensitivity	50.8 (3.1)	44.4 (2.1)	NS
SCL-90-R depression	53.3 (2.6)	47.1 (2.6)	NS
SCL-90-R anxiety	53.0 (2.6)	49.7 (2.5)	NS
SCL-90-R aggression	53.8 (2.1)	46.1 (2.7)	p<0.05
SCL-90-R phobia	51.3 (2.5)	45.3 (2.5)	NS
SCL-90-R paranoia	51.5 (2.5)	45.3 (2.23)	NS
SCL-90-R psychoticism	53.3 (2.0)	46.0 (2.2)	p<0.05
SCL-90-R global severity score	54.0 (2.3)	46.7 (2.1)	p<0.05
SCL-90-R positive symptom total	53.7 (2.0)	46.5 (1.9)	p<0.05
SCL-90-R PSDI	51.2 (2.2)	47.6 (2.4)	NS

All data are shown as mean (SEM), unless indicated otherwise.
*p Values are results of independent-samples t tests or χ^2 tests for dichotomous variables.
HADS, Hospital Anxiety and Depression Scale; NS, non-significant; PSDI, positive symptom distress index; SCL-90-R, Symptom-Checkliste von L.R. Degoratis.[20]

Subjective ratings

Following scanning, IBS patients rated the distension stimuli as significantly more painful (72±6 mm for IBS vs 33±9 mm for controls, p<0.001) and experienced significantly more overall discomfort (71±6 mm for IBS vs 45±10 mm for controls, p<0.05). On the other hand, there were no group differences in urge to defecate (75±6 mm for IBS vs 63±9 mm for controls). Furthermore, the groups did not differ significantly with respect to state anxiety, measured with the STAI-S, prior to fMRI scanning (38±2 for IBS vs 33±3 for controls) or post-scanning (37±2 for IBS vs 32±2 for controls).

In the group as a whole, neither anxiety nor depression scores were associated with rectal sensory and pain thresholds. On the other hand, both HADS scores correlated with the state anxiety response just prior to scanning (for anxiety symptoms: r=0.63, p<0.01; for depression: r=0.43, p<0.05) and following scanning (for anxiety symptoms: r=0.57, p<0.01; for depression: r=0.43, p<0.05). Furthermore, depression scores were significantly correlated with VAS ratings of perceived pain (r=0.42, p<0.05), urge to defecate (r=0.46, p<0.05), and overall discomfort (r=0.50, p<0.05) experienced during distensions. Anxiety symptoms correlated significantly with overall discomfort experienced during distensions (r=0.57, p<0.01).

fMRI results

Association of the neural response to pain with symptoms of anxiety and depression within IBS

In multiple regression analyses on patient data, anxiety scores correlated significantly with pain-induced activation of the right anterior midcingulate cortex (aMCC) (4, 18, 38; t=5.69) and pregenual anterior cingulate cortex (pACC) (4, 30, 10; t=5.75) (figure 1A, whole-brain statistics, p<0.001 uncorrected; NS after FWE correction). Depression scores were associated with pain-induced activation of left PFC (0, 18, 52; t=10.39) and cerebellar areas (−2, −70, −14; t=8.12) (figure 1B, whole-brain statistics using FWE, p<0.05).

Differences between IBS and controls in the neural response to pain

In response to painful distensions, the one-sample t test revealed activation of the right PFC, right anterior IC, left thalamus, right S1, and dorsal posterior cingulate cortex (dPCC) in IBS, and of the right anterior IC, S1 in controls (all $p<0.05$ SVC, see tables 2 and 3, figure 2). Direct group comparisons with two-sample t tests revealed activation in the IBS versus controls contrast in the left anterior IC and PFC (all $p<0.05$ SVC, see tables 2 and 3). Inclusion of anxiety and depression scores in the two-sample t tests as confounding variables led to a loss of significant group differences in the IBS versus controls contrast.

DISCUSSION

This study aimed to test the hypotheses that in IBS symptoms of anxiety and depression (1) are associated with the subjective response to painful visceral stimuli, (2) correlate with brain activation during painful rectal distensions, and (3) account for at least some of the group differences in pain-induced brain activation when compared to healthy controls. In summary, we found that anxiety and depression symptoms were associated with the extent to which distension stimuli applied in the scanner were perceived as painful. In addition, within IBS, anxiety and depression scores correlated with visceral pain-induced activation in regions of the cingulate cortex (aMCC and pACC for anxiety), and the prefrontal cortex and cerebellum (for depression). Finally, differences between IBS and controls in brain activation during visceral pain were no longer present when anxiety and depression symptoms were taken into account in the group comparisons as confounding variables. Together, these findings support the role of affective disturbances in the neural processing of visceral pain in IBS, and further underline the importance of psychological factors in the pathophysiology of visceral hyperalgesia in IBS.

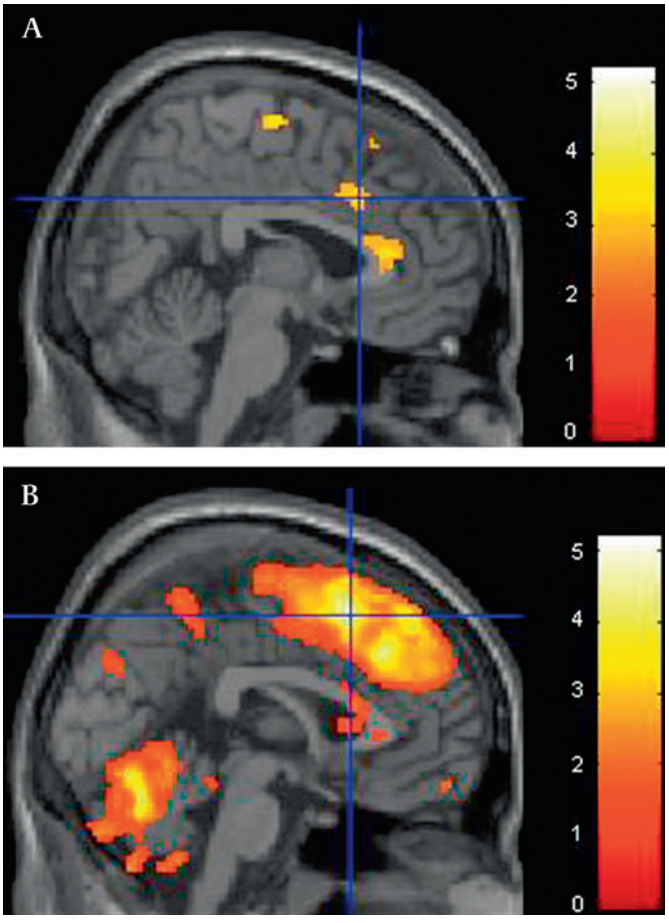

Figure 1 Correlation of HADS anxiety and depression scores with the neural response to visceral pain within IBS, computed with multiple regression analyses (whole-brain statistics whole brain, $p<0.001$ uncorrected). (A) Cortical activation during painful distensions correlating with anxiety symptoms was observed in the right anterior midcingulate cortex (aMCC) and pregenual anterior cingulate cortex (pACC). (B) Cortical activation during painful distensions correlating with symptom of depression was observed in the left prefrontal cortex and cerebellar areas. Task-related increase in the magnetic resonance (MR) signal is superimposed on sections of standard three-dimensional T1-weighted anatomical brain images.

Patients with IBS experienced markedly more pain and overall discomfort upon repeated distensions in the scanner, despite unaltered rectal sensory thresholds. Anxiety and depression were associated with these subjective stimulus ratings, but not with rectal sensory thresholds. These findings are consistent with conclusions by Dorn *et al* that increased pain sensitivity in IBS results from an increased psychological tendency to report pain, which was in turn associated with psychological distress.[2] Indeed, there is a large body of evidence supporting that the processing and evaluation of sensory information, particularly of unpleasant or painful stimuli, has important cognitive, motivational, as well as emotional components. Experimental manipulation of the emotional context, for example, with hypnosis, active relaxation, or psychological stress, affects various gastrointestinal sensory and motor functions.[3 4 6 30] In addition, expectation of pain[31] and perceived controllability of pain[32] modify perceived unpleasantness of a stimulus. Hence, one may speculate that our findings reflect an affective bias in the evaluation of painful stimuli in IBS. However, whether our findings reflect altered affective aspects of sensory perception alone remains unclear, since additional cognitive and/or motivational factors may also play a role.

Anxiety symptoms correlated with pain-induced activation of the aMCC and pACC in IBS. These results fit the established role of the ACC in the context of pain and emotion, and its relevance in disturbed neural pain responses in patients with IBS.[25 33] Interestingly, the aMCC receives high and direct input from the amygdala,[25] which has been implicated in fear[34] as well as nociception.[35] Since fear and pain sights appear to overlap in the aMCC, this region is thought to specifically mediate the fear avoidance aspect of pain processing.[25] Hence, our finding may reflect an association between anxiety symptoms and the affective–motivational components of pain processing, and one could speculate that this reflects the importance of negative emotions in the avoidance aspect of pain in IBS. Our results are supported by evidence in healthy subjects that aMCC ('dorsal ACC') activation in response to non-painful oesophageal stimuli was higher in a negative emotional condition,[13] and that selected attention to an oesophageal distension stimulus activated the aMCC ('mid-ACC').[14] The possible relevance of this specific midcingulate region for the integration of negative emotional and motivational aspects of pain processing in IBS is also underlined by recent evidence that patients with IBS and a history of abuse reported more pain, and demonstrated greater MCC/PCC activation during rectal distensions.[36] To conclude, the aMCC may mediate increased attention to visceral stimuli and pain amplification by emotions of fear and anxiety in IBS, in line with the concept of visceral hypervigilance and evidence that distention-induced MCC activity decreased during repeated stimulus exposure.[37]

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Table 2 Peak Talairach coordinates of regions significantly activated during rectal distensions in patients with irritable bowel syndrome and in controls (one-sample t test and two-sample t test)

	Talairach coordinates																	
	One-sample t test												Two-sample t test					
	IBS patients						Controls						IBS − Controls					
Region of interest	H	x	y	z	t Value*	K_E	H	x	y	z	t Value	K_E	H	x	y	z	t Value	K_E
Prefrontal cortex	R	44	43	14	5.85	96	–	–	–	–	–	–	R	28	62	−4	4.32	32
Anterior insula	R	40	10	11	8.51	234	R	38	12	3	5.59	108	–	–	–	–	–	–
Anterior insula	L	−40	8	0	4.25	23	–	–	–	–	–	–	L	−36	18	1	4.13	24
Thalamus	L	−12	−12	2	5.53	58	–	–	–	–	–	–						–
S1	R	51	−44	46	4.47	49	R	51	−42	56	6.88	37	–	–	–	–	–	–
Dorsal posterior cingulate cortex	R	2	−18	29	5.72	46	–	–	–	–	–	–						–

All coordinates were converted from MNI to Talairach space.
*All small-volume corrected $p<0.05$; for additional details, see table 3.
H, hemisphere with activation; K_E, cluster level; L, left asymmetrical activation; MNI, Montreal Neurological Institute; R, right asymmetrical activation.

Depression scores correlated with prefrontal and cerebellar activation during visceral pain. Both regions have been implicated in the neural mechanisms of depression.[38] Prefrontal regions mediate the expectancy of emotional stimuli, and the inferior and medial prefrontal cortex specifically the expectation of unpleasant stimuli.[39] Prefrontal activity is also associated with the localisation and encoding of attention to a stimulus.[40] Interestingly, emotional activation studies have revealed disturbed activation in various frontal and cerebellar regions in depressed patients,[38] and recently, patients with major depression were found to have increased prefrontal activation during heat pain.[12] Previous fMRI findings in IBS have suggested disturbed activation of prefrontal regions in IBS,[26–28 41] but have not addressed a possible correlation with depressive symptoms. Recently, Berman *et al* documented that greater rectal distension-induced activation of the right orbitofrontal cortex was associated with the amplitude of the anticipatory decrease in dorsal brainstem activation, implicating disturbances in corticolimbic inhibition.[33] Interestingly, depressive symptomatology has recently been implicated in altered central pain processing in fibromyalgia syndrome[11] and rheumatoid arthritis.[42] In rheumatoid arthritis, depression scores were correlated with medial prefrontal cortex activation during provoked joint pain, which parallels our findings in IBS.[42] Together, these findings indicate that prefrontal regions may mediate the relationship between depressive symptoms and clinical pain in patients with IBS, possibly by altering acute emotional responses. Indeed, we observed that higher depression scores were associated with greater state anxiety in the experimental situation.

As expected, the BOLD response to painful rectal distensions differed in IBS compared to healthy women. Interestingly, accounting for inter-individual differences in anxiety symptoms and depression, respectively, abolished these group differences in activation. In this context, results from the first longitudinal PET study in IBS are of interest.[37] In this study, anterior insula and bilateral thalamus remained consistently activated upon repeated distensions, whereas activation of other regions, including pregenual ACC and MCC activity, was significantly lower in the second when compared to the first session. At the same time, visceral hypersensitivity normalised.[37] The authors concluded that this reflects reduced vigilance and/or arousal to visceral stimuli in IBS. Together with our findings, these data are consistent with our hypothesis that affective disturbances and the associated negative emotional responses modulate the neural processing of visceral pain in IBS, and account for some of the group differences in pain-induced activation when compared to healthy controls. The heterogeneity of psychological characteristics and affective disturbances in patients with IBS likely constitutes an important source of variability, and may explain some of the heterogeneity of pain-related findings within the IBS imaging literature. Future studies should incorporate non-IBS controls group(s) with affective disturbances, as has recently been elegantly accomplished by Ringel and colleagues.[36]

The extent of psychological disturbances in this sample of IBS patients was relatively minor, and our findings cannot be generalised to IBS samples with more pronounced psychopathology. Rather, the present results probably reflect effects of sub-clinical impairment, as it may be commonly experienced by

Table 3 Supplementary details on region of interest analysis (one-sample t test and two-sample t-test)

Region of interest	Centre coordinate for SVC	Sphere (size, mm)	Reference	p Value whole-brain, uncorr., voxel level	p Value, SVC (FWE), voxel level
One-sample t test, IBS					
Prefrontal cortex	38, 55, 13	12	27	0.000	0.011
Anterior insula R	36, 10, 6	12	27	0.000	0.000
Anterior insula L	36, 10, 6	12	27	0.000	0.089
Thalamus	11, 14, 0	8	27	0.000	0.006
S1	51, −42, 56	12	19	0.000	0.032
Dorsal posterior cingulate cortex	−7, −23, 31	8	28	0.000	0.005
One-sample t test, controls					
Anterior insula R	−35, 13, 5	12	27	0.000	0.010
S1	51, −42, 56	12	19	0.000	0.010
Two-sample t test, IBS − controls					
Prefrontal cortex	36, 52, −6	12	29	0.000	0.026
Anterior insula L	36, 10, 6	12	27	0.000	0.037

FWE, family-wise error correction; IBS, irritable bowel syndrome; SVC, small-volume correction.

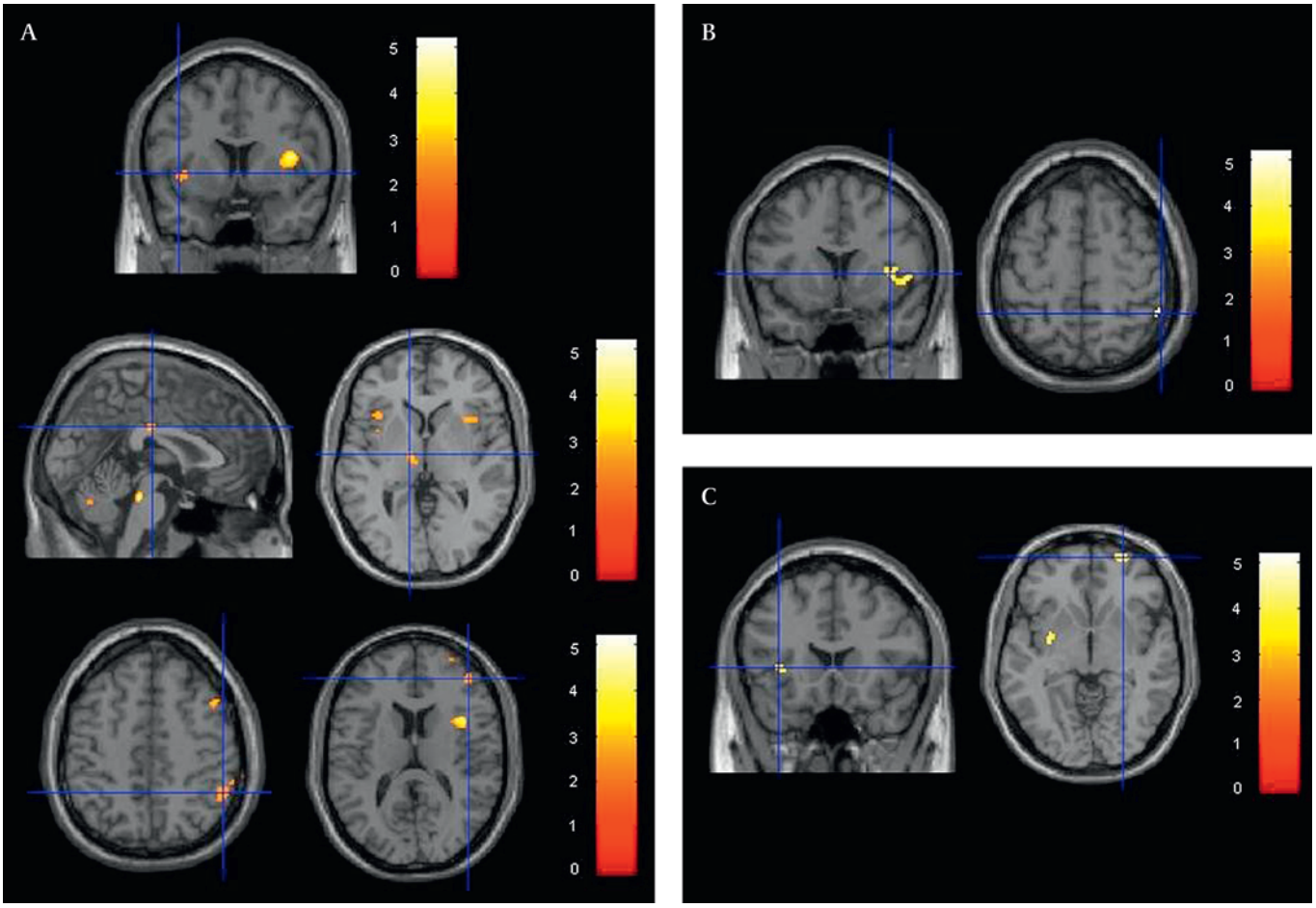

Figure 2 Cortical activation during painful rectal distensions in patients with IBS (A) and healthy controls (B), leading to group differences in the direct group comparison (C), all without consideration of HADS scores (all $p<0.05$ SVC). (A) In IBS, the one-sample t test revealed activation of the right PFC, bilateral anterior insular cortex, left thalamus, right S1, and dorsal posterior cingulate cortex. (B) In contrast, controls only showed activation of the right anterior insular cortex and right S1. (C) This led to significant group differences in the IBS versus controls contrast in the right PFC and left anterior insular cortex. Task-related increase in MR signal is superimposed on three orthogonal sections of standard three-dimensional T1-weighted anatomical brain images. HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; MR, magnetic resonance; PFC, prefrontal cortex; SVC, small-volume correction.

a significant proportion of patients with IBS.[8] Further, our sample of women with IBS was not characterised by lower rectal pain thresholds when compared to controls. This is at odds with findings in the literature, although normal discomfort thresholds[3 4] or normal pain ratings to a predefined distension pressure[36] in IBS have also been observed. Indeed, a recent study documented altered rectal perception in 61% of IBS patients,[43] which is supported by others[44–46] and the conclusion that patients with IBS show normal sensory thresholds when testing protocols are designed to minimise psychological influences.[47] Nevertheless, it is clearly important to emphasise that results from this group of patients may not reflect the neural processes mediating visceral hyperalgesia in patients with abnormally low rectal thresholds. This is particularly relevant given evidence that clinically significant anxiety may be more frequent in patients with altered rectal perception.[43] Finally, in our fMRI analyses, we statistically controlled for anxiety and depression symptoms in separate analyses, although obviously these can present as concurrent symptoms and may exert additive or synergistic effects. Clearly, future studies must expand on the present results. Nevertheless, our data support the modulation of visceral sensory signals by affective processes at the level of the brain in patients with IBS. Although this obviously does not necessarily implicate that symptoms in IBS can be entirely attributed to these processes, our findings lend further support to the role of psychological factors and specifically of affective disturbances in the pathophysiology of visceral hyperalgesia in IBS.

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