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Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls

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Abstract

Visceral pain processing is abnormal in a majority of irritable bowel syndrome (IBS) patients. Aberrant endogenous nociceptive modulation and anticipation are possible underlying mechanisms investigated in the current study. Twelve IBS patients and 12 matched healthy controls underwent brain fMRI scanning during the following randomised stimuli: sham and painful rectal distensions by barostat without and with simultaneous activation of endogenous descending nociceptive inhibition using ice water immersion of the foot for heterotopic stimulation. Heterotopic stimulation decreased rectal pain scores from 3.7 ± 0.2 to 3.1 ± 0.3 (mean $\pm$ SE, scale 0–5) in controls ($p < 0.01$), but not significantly in IBS. Controls differed from IBS patients in showing significantly greater activation bilaterally in the anterior insula, SII and putamen during rectal stimulation alone compared to rectal plus heterotopic stimulation. Greater activation during rectal plus heterotopic versus rectal stimulation was seen bilaterally in SI and the right superior temporal gyrus in controls and in the right inferior lobule and bilaterally in the superior temporal gyrus in IBS. Rectal pain scores were similarly low during sham stimulation in both groups, but brain activation patterns differed. In conclusion, IBS patients showed dysfunctional endogenous inhibition of pain and concomitant aberrant activation of brain areas involved in pain processing and integration. Anticipation of rectal pain was associated with different brain activation patterns in IBS involving multiple interoceptive, homeostatic, associative and emotional areas, even though pain scores were similar during sham distension. The aberrant activation of endogenous pain inhibition appears to involve circuitry relating to anticipation as well as pain processing itself.

Keywords: Irritable bowel syndrome; Pain; Endogenous pain inhibition; Brain; Nociception; Anticipation; Functional magnetic resonance imaging

1. Introduction

Irritable bowel syndrome (IBS) is a functional disorder defined by abdominal pain or discomfort and disturbed intestinal motility (Maxton et al., 1989; Drossman et al., 1997). A majority of patients with IBS have evidence of visceral sensory abnormalities, including lower discomfort or pain thresholds to intestinal distension and increased viscero-somatic sensory convergence compared to healthy controls (Whitehead et al., 1980; Mertz et al., 1995; Drossman et al., 1997; Munakata et al., 1997; Murray et al., 2004). The

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mechanisms behind these sensory changes are unclear, but could be driven by several sources, including persistent input from the periphery (e.g., low grade inflammation and neuroimmune activation), psychological factors (hypervigilance), as well as modifications in central sensory processing (Silverman et al., 1997; Mertz et al., 2000; Ringel et al., 2001; Delvaux, 2004; Spiller, 2004). Dysfunction of endogenous pain inhibitory mechanisms is an attractive etiological hypothesis in IBS, as this would explain modulation of sensory function by many different inputs. The main endogenous pain modulation mechanisms include the spino-bulbo-spinal feedback loop termed diffuse noxious inhibitory controls (DNIC) and the periaqueductal gray (PAG)–rostroventral medulla (RVM) network (Willer et al., 1989, 1999; Gebhart, 2004). They are central in regulating, fine-tuning and integrating pain perception and homeostatic responses. The quantification of activation of DNIC using "counterirritation" techniques has been extensively validated and relies on the perceptual modulation of a painful stimulus by a second heterotopically applied nociceptive stimulus (Pertovaara et al., 1982; Willer et al., 1989, 1999; Villanueva and Le Bars, 1995; Lautenbacher and Rollman, 1997; Washington et al., 2000; Gebhart, 2004). Using these techniques pain inhibitory mechanisms have been shown to be deficient in fibromyalgia and in our study of IBS patients (Lautenbacher and Rollman, 1997; Wilder-Smith et al., 2004). The aims of the current study were to investigate endogenous inhibitory pain mechanisms and anticipatory or vigilance effects towards visceral stimuli using sensory testing and simultaneous fMRI in patients with IBS compared to healthy controls.

2. Methods

2.1. Subjects

Twelve Chinese female IBS patients diagnosed according to the Rome II criteria were recruited from the Gastroenterology Clinic and by advertisements in the university campus, respectively (Thompson et al., 1999). The 12 healthy controls had no gastrointestinal pathology or history of abdominal pain, bowel disorders, bloating or discomfort during the last 3 months. The following exclusion criteria applied to both IBS patients and healthy controls: claustrophobia, any organic gastrointestinal, anal, hepatic or other systemic disease, lactose intolerance, bowel resections (except appendectomy) or multiple abdominal operations, a history of brain disease or surgery, ongoing treatment with any drugs or need for drugs in last 14 days, treatment with any investigational drug during the preceding 30 days, pregnancy or lactation. Controls as well as patients had not participated in any previous trials. Written informed consent was obtained from each subject. Both the National University Hospital and Singapore General Hospital Institutional Review Boards approved the study.

2.2. Experimental procedure

All test procedures described below were performed during the morning to minimize diurnal rhythm influences. The subjects first underwent the basal barostat and cold pressor stimulation tests, followed by a conditioning procedure inside the scanner and the actual fMRI session with ongoing stimulations. All subjects received identical instructions before the test sequence.

2.2.1. Rectal distention stimulation

After fasting overnight, all subjects had their rectum emptied using a water enema (300 ml warm water at 36 °C). Subsequently, a lubricated 400 ml polyethylene bag ("balloon", Mui Scientific, Toronto, Canada) attached to the top of a flexible catheter was tested for leakage by inflating with air under water and then inserted approximately 5 cm into the subject's rectum. It was then slowly inflated with air at low pressure (5 mmHg) and gently pulled back until slight resistance was felt, ensuring contact between the bag and the distal rectal ampulla. The tubing was then taped to the subject's leg. The subject was positioned on the bed in a comfortable supine position with legs slightly apart, covered with a light sheet with the knees slightly flexed and supported on pillows. After a 5-min acclimatization period, first sensation, defecatory urge and pain thresholds were determined using an ascending methods of limits protocol with incremental steps of 5 mmHg, 30 s distension and rest periods applied by a barostat (G&J Electronics Inc., Toronto, Canada) set at an inflation speed of 40 ml/s and a cut-off pressure of 60 mmHg. For subsequent rectal distensions in the study the pain detection threshold pressure plus 20% was used and subjects rated rectal pain intensity after 30 s on a 5-point Likert scale (1 = no pain, 5 = worst pain).

2.2.2. Foot cold pressor test

The left foot was comfortably positioned and immersed up to the ankle in an ice water bath maintained at 4 °C. Pain intensity was rated after 30 s on the 5-point Likert scale.

2.2.3. Heterotopic (rectal plus foot) stimulation

Cold pressor stimulation on the foot was performed simultaneously with rectal distention (heterotopic stimulation or "counterirritation") for 30 s. Subjects were asked to rate rectal pain intensity after 30 s on the 5-point Likert scale.

2.3. FMRI session

2.3.1. Stimulus timing

Following the baseline procedures described above four conditioning rectal distensions at pain detection threshold pressure plus 20% were administered inside the scanner prior to the actual experimental session to allow the subjects to familiarize themselves with the scanner environment and protocols. Subjects were informed either rectal, heterotopic or sham rectal distensions would be performed at regular intervals in random sequence and they were shielded from all cues as to which stimulus was pending. Each stimulation lasted for 30 s followed by a baseline rest period of 36 s prior to the start of the next stimulation. Each session consisted of six runs of

five stimuli each. The first stimulation within each run was always a rectal distention. The remaining stimuli within a run were randomised among the three conditions and counterbalanced across the subjects (Fig. 1). Thus, each subject received a total of 14 rectal, eight heterotopic and eight sham stimuli during the course of the whole experiment. High-resolution co-planar and 3D structural images were obtained at the end of second and fourth runs, during a 5- and 10-min break, respectively. The remaining runs were separated by breaks of 1-min duration.

Subjects were asked to fixate the centre of a monitor screen displaying a white cross on a black background as they performed the tasks. The screen turned red for 1 s before each distention as a cue for impending stimulation. At the end of each 30-s stimulation the screen turned green to prompt for the rectal pain rating relating to the previous stimulation using a five-button response box. Subjects were asked about any side-effects at the conclusion of the experimental session.

2.3.2. fMR-imaging, image analysis and statistical analysis

Imaging was performed in a Siemens 3T Allegra system (Siemens Allegra, Erlangen, Germany). Fixation cross and changing screen colors were rear-projected (Epson EMP 7250, Sydney, Australia) onto a silk screen placed at the rear of the magnet bore and participants viewed them via an angled mirror fastened to the head coil. Movement artifacts were minimized by the use of a head cage, bite-bar and specific instructions. Thirty-two oblique axial slices were acquired approximately parallel to the AC–PC line using a $T2^*$-weighted gradient-echo EPI sequence (TR = 3000 ms; effective TE = 30 ms; matrix = 64×64; FOV = 192×192 mm; 3.0 mm thickness, 0.3 mm gap). A set of co-planar high-resolution T2-weighted images was acquired in an identical orientation to the functional MR data. High-resolution anatomical reference images were obtained using a three-dimensional MP-RAGE sequence.

The functional images from each subject were preprocessed and analyzed using BrainVoyager 2000 software version 4.9 (Brain Innovation, Maastricht, Holland). Global mean intensity normalization was performed for each of the subjects. In the spatial domain, data were smoothed with a Gaussian smoothing kernel of 8 mm FWHM. A temporal high pass filter of period 170 s was applied following linear trend removal. The functional images were aligned to co-planar high-resolution images and the image stack was then aligned to a high-resolution 3D image of the brain. The resulting realigned data set was transformed into Talairach space (Talairach and Tournoux, 1988).

The expected blood oxygen level-dependent (BOLD) signal change was modelled using a gamma function (τ of 2.5 s and a δ of 1.5) convolved with the blocks of 30 s duration for each of the conditions of interest (Boynton et al.,

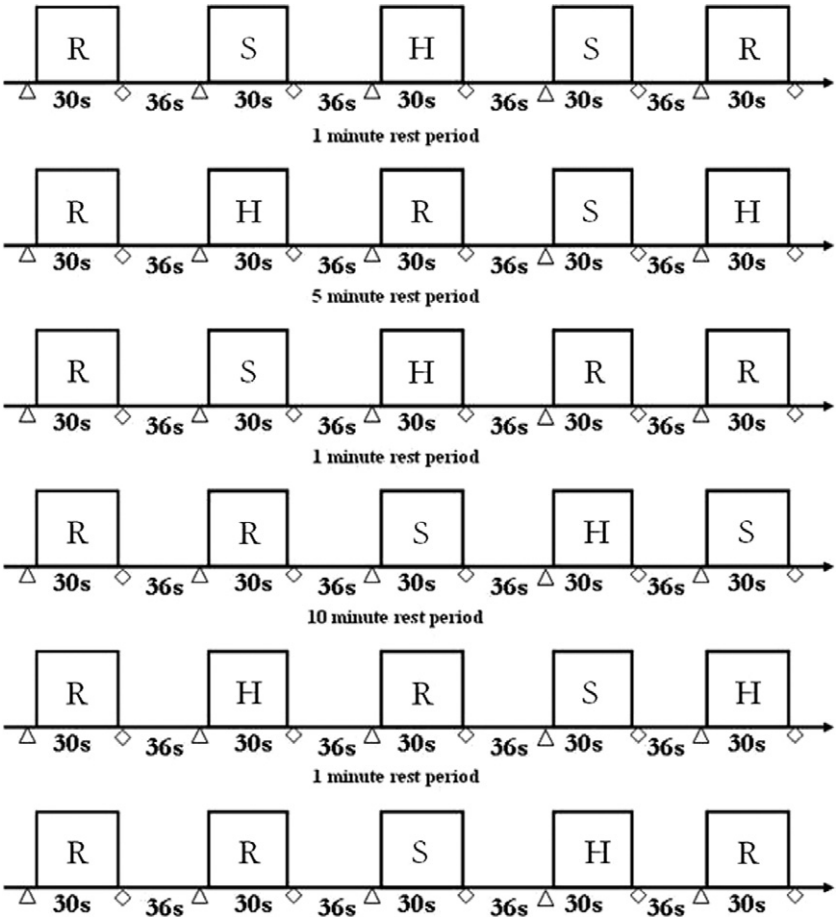

Fig. 1. An example of a stimulation session consisting of six runs with five stimuli each. R, painful rectal distention stimulation; H, heterotopic stimulation (R plus simultaneous cold pressor foot test); S, sham rectal distension. △, red light; ◇, green light.

Table 1
Rectal balloon distension sensory pressure thresholds

	First sensation (mmHg)	Defecatory urge (mmHg)	Pain (mmHg)
Healthy controls	19.6 (1.2)	36.3 (2.2)	44.6 (2.4)
IBS patients	14.6 (1.9)[a]	27.1 (2.4)[a]	34.6 (3.0)[a]

Means (standard error) are shown.
[a] $p < 0.05$, IBS patients versus healthy controls.

1996). Analysis was performed using a General Linear Model (GLM) consisting of five predictors for each subject: the three conditions of interest and two additional predictors to account for the effects of the visual cues provided to the subjects. Data across all runs of a subject were concatenated using z-transformation to account for differences in baseline across runs. The analysis for each group was carried out separately. We performed random-effect analysis at the group level and the threshold for considering a voxel significantly activated for the conditions of interest (rectal, heterotopic and sham for each of the groups) against baseline was $p < 0.001$ corrected. We also looked at significant differences between activation for rectal versus heterotopic, heterotopic versus rectal, sham versus rectal, as well as rectal versus sham conditions for each of the groups using a direct contrast between the conditions using random-effect analysis at $p < 0.001$, uncorrected.

All additional statistical analyses were performed using standard SPSS package (Version 12.0 for Windows, Chicago, America). Continuous variables were expressed as arithmetic mean ± standard error, and categorical variables were expressed as frequencies and percentages. Variables that were not normally distributed were transformed by logarithmic transformation to satisfy normality assumptions. Non-parametric data were analyzed using the Mann–Whitney U test. To compare the differences between IBS and healthy control groups, chi-squared test was used for categorical variables and independent samples t-test for continuous variables. A two-tailed p-value <0.05 was considered statistically significant.

3. Results

Twelve IBS patients (mean age, 23 years; SE, 0.39), six constipated and six diarrheic IBS with at least 2 years duration of active IBS, and 12 Chinese age-matched female healthy controls (mean age, 23 years; SE, 0.92) were recruited.

3.1. Rectal distension and cold pressor test

All rectal distension pressure thresholds in IBS patients were significantly lower than those in normal controls ($p < 0.05$) (Table 1).

Rectal pain scores in healthy controls were significantly lower during heterotopic stimulation than during rectal distention alone ($p < 0.01$) and also lower than during heterotopic stimulation in IBS patients ($p < 0.01$) (Table 2). The decrease in rectal pain score by addition of heterotopic stimulation (R minus H) was also significantly greater in controls than in IBS patients ($p < 0.01$) (Table 2). Pain ratings during the foot cold pressor test, sham stimulation and the rectal distention alone were not significantly different between patients with IBS and healthy controls (Table 2).

3.2. Brain fMRI

Significant activations and deactivations in controls and IBS patients are shown in Tables 3 and 4 and Figs. 2–4. Common activations in control and IBS groups during both rectal pain with and without heterotopic stimulation were demonstrated in the anterior precentral gyrus and anterior insula bilaterally, the left thalamus, left cerebellum and Brodmann areas 6 and 32, the anterior cingulate cortex and supplementary motor area (SMA), and pre-SMA in the rectal and heterotopic conditions. The healthy controls additionally activated the bilateral superior frontal gyri, left middle frontal gyrus, right posterior thalamus, right SI, bilateral SII and left inferior parietal lobule during rectal stimulation (Fig. 2a). During heterotopic stimulation only controls showed significant activation in bilateral superior frontal gyri, left middle frontal gyrus, bilateral putamen, left SI, and left inferior parietal lobule, whereas IBS patients showed unique additional activation in the right SII area (Fig. 2b). Multiple differences in activations were seen during sham stimulation, even though there were no differences in sham distension pain ratings between groups. Controls differed from IBS subjects in having increased activation in bilateral precentral gyri, right superior frontal gyrus, and bilateral putamen, as well as diminished activation in bilateral hippocampi (Fig. 2c). IBS

Table 2
Pain intensity ratings during different stimuli on 5-point Likert scale (1 = no pain, 5 = worst pain)

	Foot pain during C	Rectal pain during R	Rectal pain during H	Rectal pain during S	Δ Rectal pain (R minus H)
Healthy controls	4.6 (0.1)	3.7 (0.2)	3.1 (0.3)[b]	1.1 (0.0)	0.6 (0.2)
IBS patients	4.8 (0.1)	4.1 (0.2)	4.1 (0.2)[c]	1.1 (0.1)	0.0 (0.2)[a]

Means (standard error) are shown. C, foot cold pressor test; R, rectal distention; H, heterotopic stimulation (rectal distention plus foot cold pressor test); S, sham rectal distension.
[a] $p < 0.05$, IBS patients versus healthy controls for R minus H.
[b] $p < 0.01$, healthy controls H versus R.
[c] $p < 0.01$, IBS patients versus healthy controls during H.

Table 3
Peak Talairach coordinates of regions significantly activated during rectal, heterotopic and sham stimulation in healthy and IBS subjects

Region of interest	BA	Talairach coordinates									
		Control group					Patient group				
		H	*x*	*y*	*z*	*t*-value	H	*x*	*y*	*z*	*t*-value
Rectal stimulation											
Supplementary motor area	6	–	−3	14	55	9.06	–	1	14	50	7.97
Anterior cingulate cortex	32	–	−9	14	40	12.79	–	–	–	–	[a]
Inferior frontal gyrus	44	B	51	12	16	11.03	B	51	10	5	9.17
Superior frontal gyrus	9	B	−30	44	31	11.19		–	–	–	
Middle frontal gyrus	10	L	−37	47	7	7.73		–	–	–	
Anterior insula	13	B	33	26	1	12.72	B	−31	19	10	5.49
Thalamus (posterior)	–	B	−9	−13	7	8.39	L	−15	−13	12	11.42
Putamen	–	B	−24	−3	6	8.15	B	−18	−1	13	8.35
Postcentral gyrus (S1)	2	B	−48	−24	37	4.96	L	−45	−24	46	8.32
SII	2	B	−57	−19	25	5.816		–	–	–	
Inferior parietal lobule	40	B	60	−34	40	9.64	R	47	−49	49	3.95
Cerebellum	–	L	−29	−63	−23	4.96	L	−36	−61	−18	5.64
Deactivations											
Hippocampus	–	B	27	−14	−14	−6.58	B	−24	−14	−8	−8.56
Posterior cingulate	7	–	3	−55	30	−10.02	–	0	−40	40	−17.76
Anterior cingulate	32	–	2	40	−3	−7.75	–	0	50	1	−6.65
Heterotopic stimulation											
Supplementary motor area	6/32	B	−6	19	46	6.19	B	0	11	46	8.09
Inferior frontal gyrus	44	B	51	14	19	6.31	B	48	17	2	8.88
Superior frontal gyrus	9	B	−33	44	33	5.93		–	–	–	
Middle frontal gyrus	10	L	−39	49	18	5.09		–	–	–	
Anterior insula	13	B	36	17	4	8.6	B	−36	17	7	5.03
Thalamus (posterior)	–	L	−6	−16	5	4.69	L	−12	−13	10	6.01
Putamen	–	B	−18	−1	10	4.34		–	–	–	
SII	40		–	–	–		R	64	−19	20	4.17
Inferior parietal lobule	40	L	−48	−46	50	5.64		–	–	–	
Cerebellum	–	–	1	−40	−12	7.36	L	−3	−70	−9	6.64
Deactivations											
Hippocampus	–	B	27	−11	−14	−7.16	B	27	−26	−8	−7.06
Posterior cingulate	7	–	6	−55	32	−13.04	B	5	−43	41	−9.2
Anterior cingulate	32	–	1	43	1	−6.32	B	−3	41	−5	−7.33
Sham stimulation											
Supplementary motor area	6		–	–	–		B	8	26	48	10.03
Anterior cingulate cortex	32	–	9	18	42	7.70		–	–	–	[a]
Precentral gyrus	44	B	54	15	19	10.72		–	–	–	
Superior frontal gyrus	9	B	45	37	28	7.33	B	39	17	37	7.1
Middle frontal gyrus	10	B	33	42	15	11.04	B	35	48	5	13.76
Anterior insula	13	B	33	17	10	13.87	B	36	18	1	6.51
Putamen	–	B	24	−2	10	5.82	B				
Postcentral gyrus (S1)	2		–	–	–		B	−45	−30	45	7.36
Inferior parietal lobule	40	B	57	−39	45	6.59	L	−36	−52	52	7.00
Deactivations											
Hippocampus	B	−23	−18	−11		−10.11		–	–	–	
Posterior cingulate	–	−3	−49	25		−6.04		–	–	–	

For bilateral activations, the coordinates shown refer to the stronger activation of the two hemispheres.
IBS, irritable bowel syndrome; BA, Brodmann areas; H, hemisphere with activation; B, bilateral activation; R, right asymmetrical activation; L, left asymmetrical activation.
[a] The peak of activation in the anterior cingulate region was not separable from the peak in the supplementary motor area.

showed unique increased activation in the right middle frontal gyrus and left SI.

Activation differences between stimulation conditions were assessed for each subject group, eliminating background confounders, such as anticipation (Table 4). Unique differences in brain activation patterns between subject groups become apparent in the rectal versus heterotopic stimulation comparison in the anterior insula, SI, SII and putamen in controls and in the precuneus and inferior parietal lobules in IBS. Multiple differences in activation areas emerged between rectal and sham distension conditions, with unique changes in bilateral

Table 4
Significant differences in brain fMRI activations between stimulation conditions for healthy controls and IBS patients

Regions	BA	Healthy controls	IBS patients
Rectal minus heterotopic			
Insula (anterior)[a]	13	+Bilateral	
Postcentral Gyrus (SII)[a]	40	+Bilateral	
Putamen[a]	–	+Bilateral	
Inferior frontal gyrus	44	+Bilateral	+Bilateral
Caudate head	–	–	−Bilateral
Thalamus	–	+Left	+Left
Heterotopic minus rectal			
Parietal lobule (SI)[a]	1	−Left	
Precuneus (Medial)[a]	7		−Right
Inferior parietal lobule[a]	40		+Right
Superior temporal gyrus	39	+Right	+Right
Rectal minus sham			
Inferior frontal gyrus[a]	44	+Bilateral	
Insula (anterior)[a]	13	+Right	
Inferior parietal lobule[a]	40	+Bilateral	
Superior frontal gyrus[a]	6	+Right	
Supplementary motor area	6	+Bilateral	+Bilateral
Anterior cingulate cortex	32	+Bilateral	+Bilateral
Precentral gyrus[a]	6		+Bilateral
Thalamus	–	+Bilateral	+Bilateral
Inferior Parietal Lobule	40	+Right	+Right
Sham minus rectal			
Occipital lobe, cuneus[a]	18	−Bilateral	
Middle temporal gyrus[a]	39	−Bilateral	
Precuneus[a]	7	−Bilateral	
Superior parietal lobule[a]	7		+Bilateral
Middle frontal gyrus[a]	10		+Bilateral
Middle temporal gyrus[a]	21		−Bilateral
Parahippocampal gyrus[a]	36	−Bilateral	−Bilateral

+, significant activation; −, significant deactivation. IBS, irritable bowel syndrome; BA, Brodmann areas.
[a] Main healthy controls versus IBS patient differences.

inferior frontal gyri, bilateral anterior insulae, bilateral parietal lobules and right superior frontal gyri, bilateral occipital lobes, cunei, middle temporal gyri and precunei in healthy controls and in the bilateral superior parietal lobules, middle frontal, middle temporal and parahippocampal gyri in IBS (Table 4).

4. Discussion

The present study investigated brain activation patterns during stimulation of endogenous pain-modulating mechanisms in IBS patients and healthy controls. Quantitative sensory testing showed that pain modulation activated by heterotopic stimulation was effective at reducing rectal pain in healthy controls, but not in IBS. When the components of heterotopic stimulation, the individually titrated rectal distension and foot cold pressor tests, were applied separately similar pain levels were attained in both subject groups. The pain suppressing effect of heterotopic stimulation in healthy controls is well documented and has been demonstrated with ischemic, electrical as well as heat and cold pain (Pertovaara et al., 1982; Willer et al., 1989; Washington et al., 2000). Heterotopic stimulation activates DNIC, which constitute a spino-bulbo-spinal loop involving ascending pathways in the anterolateral spinal columns, integration in the lower brain stem, and descending influences reaching the dorsal horn neurons (Willer et al., 1989, 1999). Higher cortical regions appear to be tightly functionally coupled to the descending modulatory pathways (Lorenz et al., 2003; Ohara et al., 2005). Neuroanatomical studies suggest functional linking of the PAG with the frontal cortex, dorsolateral frontal cortex, hypothalamus, anterior insula, amygdala, as well as several brainstem nuclei (Dubner and Ren, 1999; Fields and Basbaum, 1999; Willer et al., 1999). In the current study many of these areas involved in secondary pain processing showed decreased activation during heterotopic stimulation in healthy controls, but not in IBS patients. They included the supramarginal gyri (SII), putamen and anterior insula, thalamus and frontal cortex (Talbot et al., 1991; Coghill et al., 1994; Silverman et al., 1997; Bonaz et al., 2002; Inui et al., 2003; Bingel et al., 2004; Wilder-Smith et al., 2004; Brooks et al., 2005; Mayer et al., 2005). The putamen appears to play a role in somatotopic pain processing, pain related motor responses, memory and learned behaviors (Bingel et al., 2004; Brooks et al., 2005). It is coextensive with the insula, which is of major importance in interoceptive homeostatic function, including the processing of pain, and integration with the autonomic nervous system (Treede et al., 1999; Craig, 2003). Recent evidence supports the early involvement of SII in pain perception and the differentiation between visceral and somatic pain (Hiraga et al., 2005; Hobson et al., 2005; Strigo et al., 2005).

During heterotopic stimulation brain activation patterns in IBS patients differed from controls in the frontal lobe, anterior insula, putamen, SI, SII and dorsolateral prefrontal cortices. Consequently, many of the areas involved in endogenous modulation in healthy controls showed abnormal activation patterns in IBS, supporting the concept of abnormal descending modulation in IBS. Areas relating to intensity coding of stimuli, such as the anterior insula and the postcentral gyrus, showed diminished activation with heterotopic stimulation in controls but not in IBS. Conversely, increased activation in the right dorsolateral prefrontal cortex with heterotopic stimulation was only seen in IBS, possibly linked to deviant modulation of midbrain–thalamic pain input (Lorenz et al., 2003).

The dysfunctional pain modulation in IBS patients reproduces the results of an earlier pilot study (Wilder-Smith et al., 2004). To our knowledge no other investigations of endogenous pain modulation pathways in IBS have been published, except a recent paper using

a somatic cutaneomuscular flexion reflex (RIII-reflex), which suggested hyperexcitability of spinal sensory processes in a subgroup of IBS patients (Coffin et al., 2004). Dysfunctional pain modulation has been demonstrated in fibromyalgia, a condition often associated with IBS (Lautenbacher and Rollman, 1997).

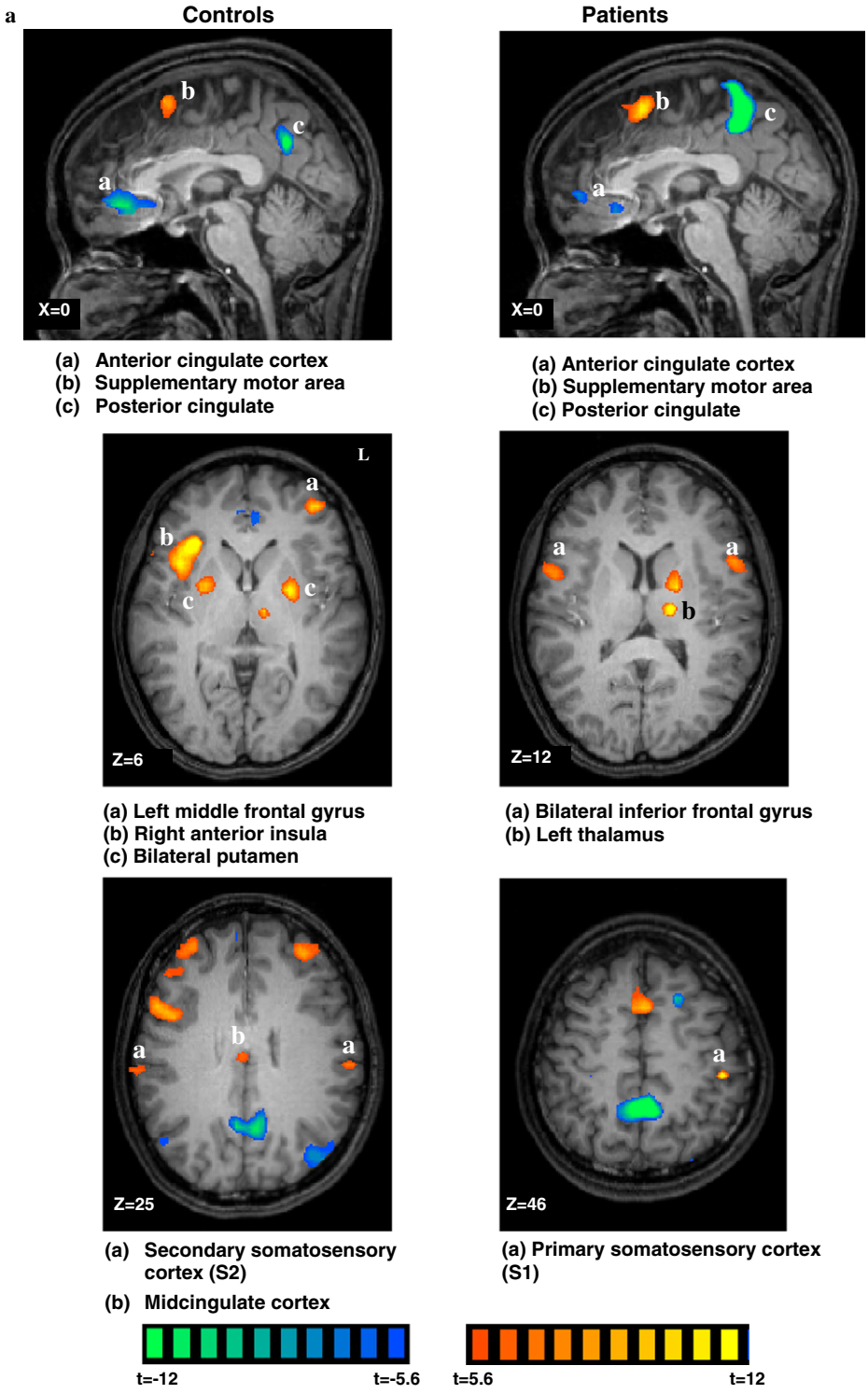

Fig. 2. Regions showing significant activation changes (random effects $p < 0.001$ uncorrected) during painful rectal distension (a), rectal distension and heterotopic stimulation (b) and sham painful rectal distension (c) in healthy controls (left column) and IBS patients (right column). The z-values represent the Talairach z-coordinate of the slice shown. A region in orange indicates increased activation compared to baseline while blue indicates decreased compared to baseline. The main areas with significant activation changes are labelled.

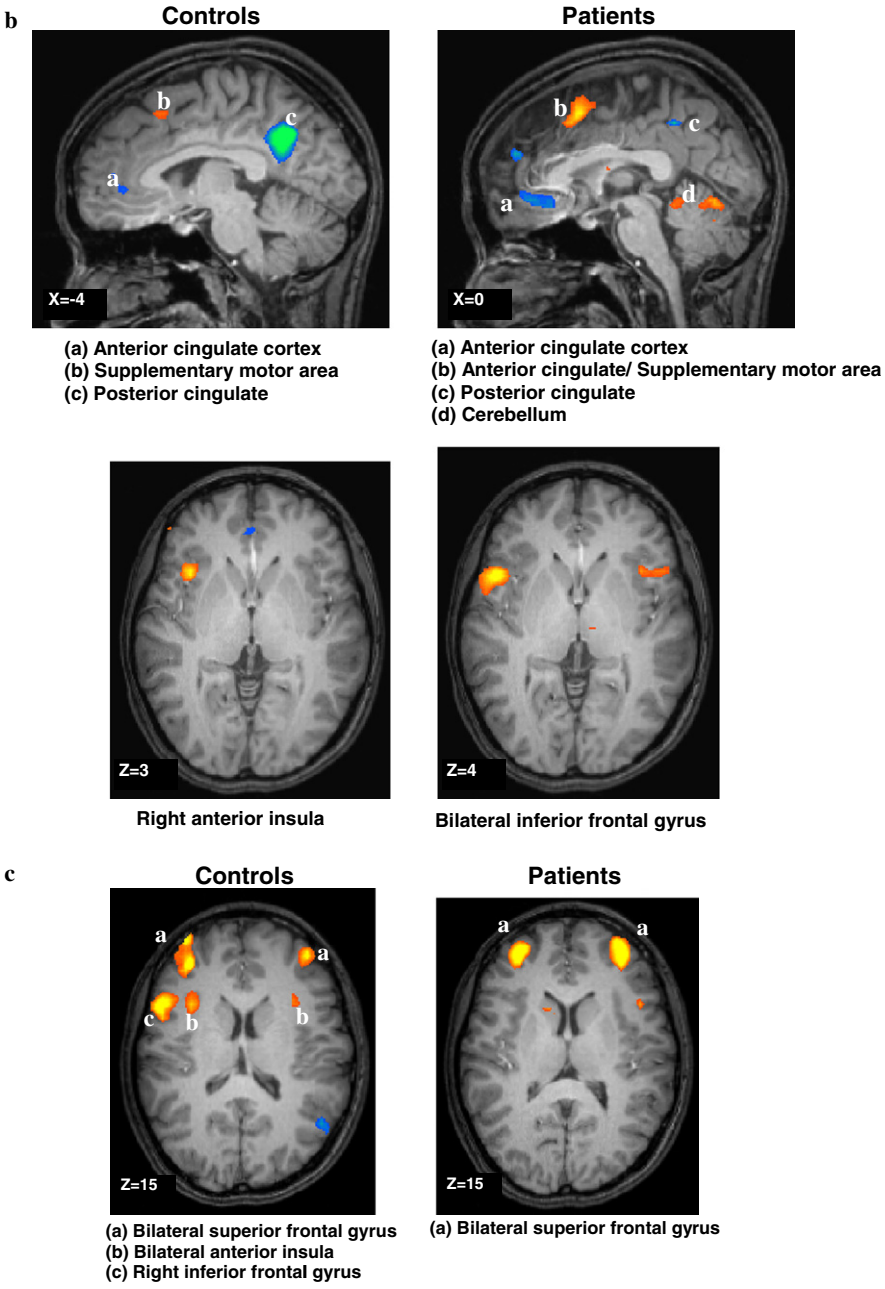

Fig. 2 (*continued*)

Mental attention focussed away from the painful stimulus (or distraction) has also been shown to diminish pain and to downregulate activation in the neuromatrix of pain, including the insula, thalamus and several divisions of the cingulate cortex (Longe et al., 2001; Bantick et al., 2002). The distinction of attentional and direct brainstem modulatory effects on pain is problematic due to the widespread integration of the pain matrix and the considerable overlap between the attentional and the pain processing matrices (Peyron et al., 1999; Bantick et al., 2002). The frontal lobe is central to attentional processes and the dorsolateral and prefrontal cortices exert powerful modulatory control over cortical and subcortical nociceptive pathways (Peyron et al., 1999; Longe et al., 2001; Bantick et al., 2002; Lorenz et al., 2003; Ohara et al., 2005). In the current study attentional effects were assessed by comparing sham with actual rectal stimulation within a blinded and randomised sequence. This comparison in healthy controls showed attentional effects were predominantly localised in the anterior cingulate cortex (Brodmann 32), the supplementary motor area (Brodmann 6), the premotor cortex, the frontal gyri, the putamen and the left dorsolateral prefrontal cortex. These areas mainly relate to

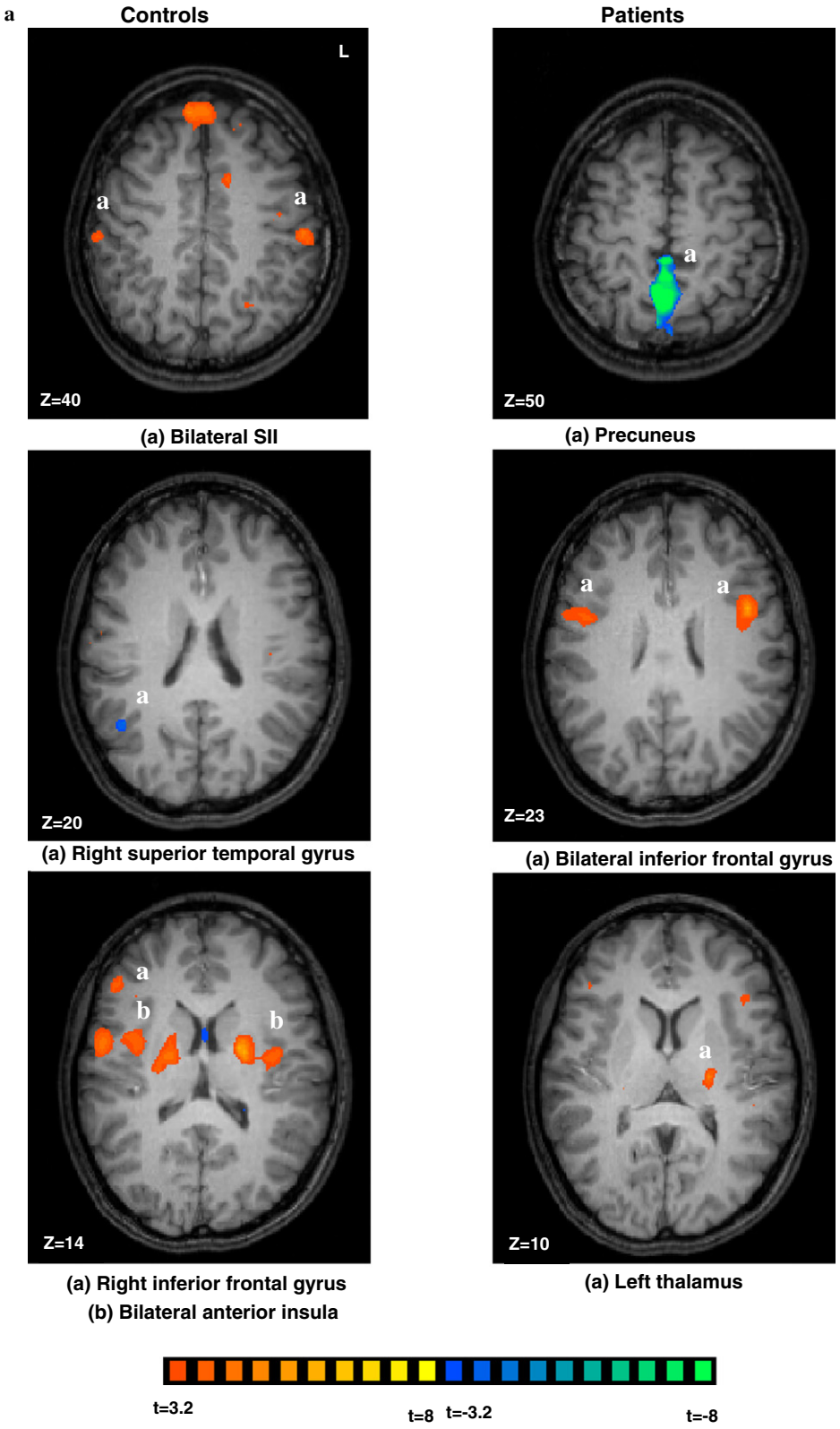

Fig. 3. (a) Regions showing significant differences (random effects $p < 0.001$ uncorrected) between painful rectal and heterotopic stimulations in healthy controls (left column) and IBS patient (right column) groups. The z-values represent the Talairach z-coordinate of the slice shown. A region in orange indicates greater activation for rectal compared to heterotopic while blue indicates greater activation for heterotopic. (b) Time–activity curves from the right and left anterior insula in healthy controls. Stimulation lasted from time points 0 to 10. Het, heterotopic stimulation (rectal plus foot). (c) Time–activity curves from the right and left SII region in healthy controls. Stimulation lasted from time points 0 to 10. Het, heterotopic stimulation (rectal plus foot).

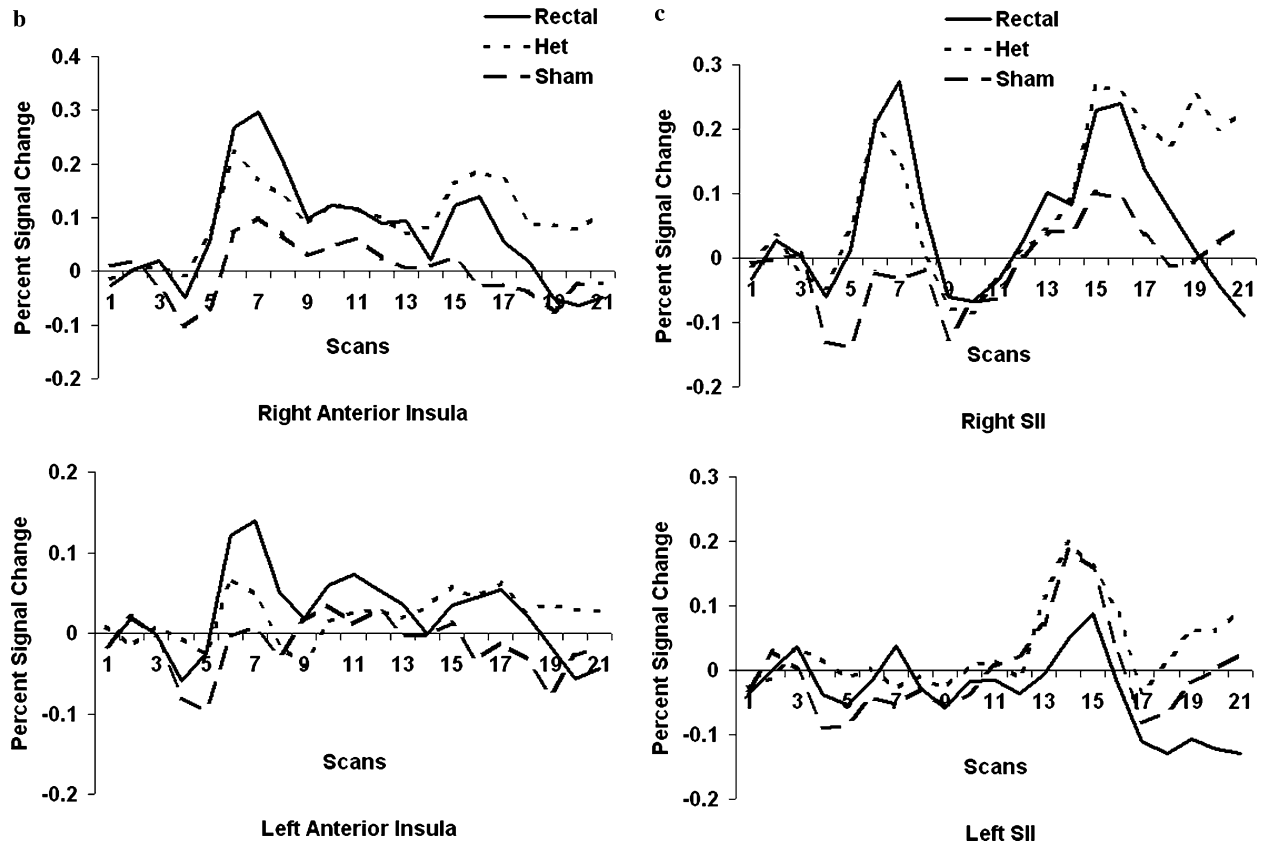

Fig. 3 (*continued*)

cognitive, coordinative function, including motor patterns and link autonomous mechanisms with descending inhibition. When contrasting specific activations due to heterotopic stimulation (heterotopic minus rectal stimulation analysis) with those attributable to attentional effects the only overlap was seen in the superior temporal gyrus (Brodmann area 39), which was classified as part of the attentional network by Peyron et al. (1999). It thus appears attentional effects alone do not explain the pain reduction due to heterotopic stimulation. A direct comparison between a physical painful and an attention-modulating heterotopic stimulation was not performed in this study and thus a clearer distinction is not possible. Indeed, such a protocol would be difficult to implement due to the inherent attentional effects of a second stimulus on the one hand and artifacts due to non-specific mental processes on the other.

Although IBS patients showed similar pain scores to controls during sham stimulation, the accompanying brain activation patterns differed considerably in frontal and posterior parietal regions, areas closely implicated in attentional functions as well as vigilance, cognition, motor coordination, memory, emotional and sensory association (Yamasaki et al., 2002; Penner et al., 2003). Regions associated with intensity coding, such as the thalamus, anterior insula, postcentral gyrus, showed similar activation patterns in both groups. These data may be taken to support a dysfunction in attentional rather than discriminative circuitry in IBS and involves some of the same frontal lobe centres dysfunctional during heterotopic stimulation.

The main differences during rectal distension alone were evident in the frontal lobe, thalamus, dorsolateral prefrontal and SII cortices. This corresponds to areas reported in previous studies and our own pilot investigation, but there are some differences in activation areas, most notably in the ACC, which may be explained by several adaptations to the protocol. These include the speed and duration of balloon distension, the imaging technique and analysis and the selection and ethnicity of the subjects. Many previous publications have investigated the effects of rectal distension on fMRI and excellent summaries have recently been published (Derbyshire, 2003; Kwan et al., 2005).

Possible limitations of the present study are, first, the exclusion of brain stem imaging from this study, as brain stem activations are of prime importance in studies of endogenous pain modulation. However, current fMRI techniques cannot be reliably used to visualize this area due to extensive artifacts. Very recently a new fRMI technique for this explicit purpose has been described (Dunckley et al., 2005). Second, documenta-

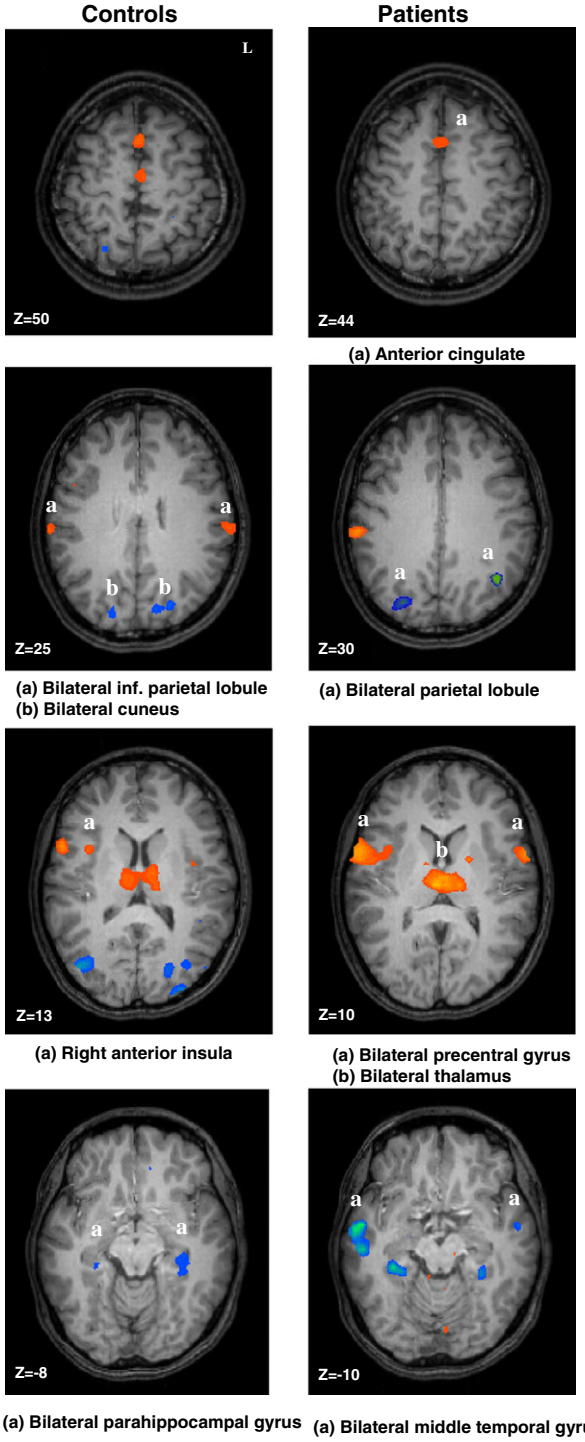

Fig. 4. Regions showing significant differences between rectal and sham stimulations in normal controls (left column) and IBS patients (right column). The *z*-values represent the Talairach *z*-coordinate of the slice shown. A region in orange indicates greater activation for rectal compared to sham while blue indicates greater activation for sham. See Fig. 3a for *t*-score scale.

tion of anxiety levels throughout the study would have been useful for correlation with group effects. Anticipatory anxiety effects on the imaging data, however, were controlled for both by baseline correction and by sham subtraction analysis. Third, assessing the reproducibility of the activation patterns was not part of the study protocol. Although recent data show encouraging concordance in repeat studies, further confirmation of adequate reproducibility is important.

In conclusion, endogenous modulation of visceral pain is abnormal during heterotopic stimulation in IBS. Activation of multiple brain areas during descending nociceptive modulation in controls differed significantly from IBS patients, with failure to downregulate in nociceptive areas and upregulation in a prime modulatory centre. Some of the affected brain regions are part of the attentional circuitry of the brain, implying their involvement in pain modulation in healthy controls, but also malfunction in this circuitry in IBS. The divergent fMRI activation patterns in IBS versus healthy subjects during sham stimulation provided further support for a predominant central dysfunction in integrative, cognitive processing of visceral pain in IBS.

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