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Quantitative Meta-Analysis Identifies Brain Regions Activated during Rectal Distension in Irritable Bowel Syndrome

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Abstract

Background and Aims—The responsiveness of the central nervous system (CNS) is altered in patients with irritable bowel syndrome (IBS). However, due variations in experimental paradigms, analytic techniques, and reporting practices, little consensus exists on brain responses to visceral stimulation. We aimed to identify brain regions consistently activated by supraliminal rectal stimulation in IBS patients and healthy subjects (controls), by performing a quantitative meta-analysis of published studies.

Methods—Significant foci from with-in group statistical parametric maps were extracted from published neuroimaging studies that employed rectal distension. Voxel-based activation likelihood estimation was applied, pooling the results and comparing them across groups.

Results—Across studies, there was consistent activation in regions associated with visceral afferent processing (thalamus, insula, anterior mid-cingulate) among IBS patients and controls, but considerable differences in the extent and specific location of foci. IBS patients differed from controls in: 1) More consistent activations in regions associated with emotional arousal [pregenual anterior cingulate cortex (pACC), amygdala]; 2) Activation of a midbrain cluster, a region playing a role in endogenous pain modulation. Controls showed more consistent activation of the medial and lateral prefrontal cortex.

Conclusions—Patients with IBS have greater engagement of regions associated with emotional arousal and endogenous pain modulation, but similar activation of regions involved in processing of visceral afferent information. Controls have greater engagement of cognitive modulatory regions. These results support a role for CNS dysregulation in IBS. These findings provide specific targets for guiding development of future neuroimaging protocols to more clearly define altered brain-gut interactions in IBS.

Keywords

Irritable bowel syndrome; neuroimaging; visceral pain

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Introduction

IBS is one of the most common persistent pain syndromes, characterized by chronic abdominal pain or discomfort and associated alterations in bowel habits. It is thought to result from a complex dysregulation of bidirectional brain-gut interactions.[1, 2] Disease models were initially developed based on patient subjective reports of pain and discomfort, with observed modulation of symptoms and perceptual responses by stressful life events and experimental stressors respectively. Over the last decade, experimental paradigms utilizing various brain imaging techniques have supported as well as expanded these initial models, demonstrating that alterations in central sensory processing/modulation exist in IBS subjects [3–7] For example, we have previously reported evidence to suggest that activity in brain regions associated with pain modulation, attention, and emotional arousal appear to differ between IBS and healthy control subjects (controls) in conditions of controlled rectal distension.[7–9] Most importantly, these differences could not be fully explained by the presence of *visceral* hypersensitivity (e.g. increased afferent input from the gut), as similar differences have been observed even in sham conditions or during the anticipation period before a visceral stimulus. Overall, neuroimaging findings suggest that IBS subjects appear to engage greater limbic regions in response to a real or potential visceral stressor, compared to controls.

Despite the growing body of literature on brain responses to visceral stimulation, reaching a consensus about published data has proved difficult due to the variety of experimental paradigms utilized (including subliminal, percept-related and stimulus related), analytic techniques, and reporting practices. Previous reviews of brain imaging studies using visceral stimulation have relied on low-powered conventional vote counting procedures to determine the brain regions activated consistently across studies.[10–12] Derbyshire et al. reported on visceral stimulation studies in IBS and controls performed from 1997 to 2001 with PET or fMRI.[11] This systemic review suggested that the most consistent activations seen across all subjects were in the insula, prefrontal, anterior cingulate, and primary sensory cortices and that differences between controls and IBS patients were localized to primary and secondary somatosensory cortices (S1, S2) and Brodmann area (BA) 39/40. Two more recent reviews also report activation of thalamus response to visceral stimulation in controls and IBS.[10, 13]

Newly emerging meta-analytic techniques for neuroimaging employ statistical analyses to empirically test and complement narrative literature reviews. [14–16] Activation Likelihood Estimation (ALE) has become the most prominent method of creating pooled analyses of neuroimaging data. Rather than simply counting the presence or absence of brain activity in an entire region of interest, these analyses incorporate the specific coordinates reported from individual studies to better determine convergent areas reliably activated across multiple studies. This allows for use of whole brain results, avoids potential disagreement in region of interest classification, and allows for determination of the statistical probability of cluster significance, rather than the descriptive reports of tabulation based studies.

The aim of this study was to apply a quantitative meta-analytic technique, ALE, to localize the brain regions most consistently activated during supraliminal lower gastrointestinal stimulation in IBS subjects and controls. We hypothesized that IBS subjects would display greater activity within regions involved in visceral afferent processing, emotional arousal and attention. We demonstrate that consistently activated brain regions can be reliably identified in control and IBS subjects undergoing lower gastrointestinal stimulation, despite the wide variety of study designs and subject inclusion criteria. In addition, we found significant differences between IBS and control subjects, most prominently in regions associated with emotional arousal and endogenous pain modulation, as well as in regions concerned with visceral afferent processing These findings are consistent with group

differences in several neural networks we have previously hypothesized to be relevant in IBS pathophysiology.

Methods

Inclusionary/exclusionary criteria

Studies were included in the meta-analysis if the experimental design included supraliminal rectal balloon distension in male and/or female IBS subjects or controls. Supraliminal rectal distension in this setting includes both painful and non-painful stimuli. The analysis included both fMRI and PET studies. Foci were extracted from the results of with-in group analyses. Only activated foci were considered for analysis because deactivations were not consistently reported. Studies were excluded if the results were obtained after or during medical or psychological treatment (including placebo) or purposeful mood induction. Not all studies meeting inclusionary criteria reported within group analyses or specific information on significant foci. In these instances study authors were contacted regarding the data, and if available it was included. If data from the same sample was reported in more than one publication, only one publication was included in the analysis.

Statistical Analyses

A voxel-based ALE meta-analysis was applied to pool the results of multiple studies.[14] Details of the mathematical algorithms can be seen in Turkeltaub 2002.[16, 17] Briefly, given the uncertainty in reported spatial coordinates from a manuscript, each foci is treated as a probability distribution centered about a peak at the reported coordinate. The activation foci were modeled as the peaks of 3-D Gaussian distributions with a full-width half-maximum of 10 mm. The ALE statistic, representing the probability that at least one of the activation foci lies within a given voxel, was calculated at each voxel. A nonparametric permutation test was applied to test the null hypothesis that the foci are spread uniformly throughout the brain.[18] A false discovery rate (FDR) of p=.05 was applied to threshold p values obtained from 5000 permutations for the ALE map. FDR controls the expected proportion of false positives among the suprathresholded voxels. The FDR threshold was determined from the observed p-value distribution, and hence is adaptive to the amount of signal in the data. ALE was used to pool and compare the results from IBS and controls. The minimum volume used to define a cluster was set to 100 mm^3. Calculation of ALE statistics, permutation testing, thresholding, and cluster analysis were carried out with GingerALE Version 1.1 and 2.0 (www.brainmap.org).[14] With-in group analyses were generated using random-effects approach in GingerALE version 2.0 which essentially weights the between subject variance for each study by sample size. Subtraction analyses were performed using the fixed-effects algorithm implemented in GingerALE version 1.1. We limit our interpretation of the subtraction analysis to regions identified in with-in group random effects analysis. Anatomic regions were labeled using the Talairach Daemon[19] for all but the cingulate subregions, which were based on those described by Vogt et al. [20] Conjunction analysis for group results was performed by multiplying binarized versions of the thresholded ALE maps obtained for the within group analyses using FSLmaths. Because each of these maps was tested using a FDR of p=.05, this conjunction tests against the conjunction null at $p < .05$ (FDR). We overlayed the resultant conjunction map onto an anatomical template in Talairach and Tournoux (1988) space to visualize cluster overlays.[21]

Results

Studies meeting inclusionary criteria

18 studies [4, 7, 22–37] yielded tabulated coordinates for 13 inflation contrasts in IBS subjects and 12 inflation contrasts for control subjects (detailed in Table 1). The ALE analysis of IBS subjects incorporated 161 foci and the control subject analysis used 147 foci.

Brain regions associated with lower gastrointestinal stimulation in healthy control subjects

The within group analysis for control subjects is presented in Table 2 and Figure 1. Regions consistently activated in response to supraliminal lower gastrointestinal inflation across healthy control studies included those associated with visceral sensation [Bilateral (B) anterior insula (aINS), B anterior midcingulate cortex (aMCC), and right (R) thalamus], emotional arousal (R pACC, BA 32), and regions associated with attention and modulation of arousal [left (L) inferior parietal (BA 40), L lateral (BA 9/46) and R medial prefrontal cortex (BA 9/32)]. In addition consistent activation was seen in the putamen and the post central gyrus (BA 43).

Brain regions associated with lower gastrointestinal stimulation in IBS subjects

Significant consistent activations were observed in response to supraliminal lower gastrointestinal inflation for IBS subjects, in regions associated with visceral afferent processing (B a/mINS, B aMCC, B thalamus), emotional arousal (L amygdala, R inferior pACC) and attention (BA 6). A large midbrain region was also identified, and while it appears midline in the summary image, this region is the product of several more bilaterally positioned foci from 4 individual studies. While the spatial resolution in the brain stem is suboptimal across the included studies, foci comprising this region may include the nucleus cuneformis, red nucleus or periaqueductal gray (PAG). Consistent activations were also seen in the cerebellum and R Putamen. (see Table 3, Figure 2).

Group comparisons

Group comparisons of brain regions consistently activated across studies can be seen in Table 4, and Figure 3. Conjunction analysis showed that regional overlap was evident in the right thalamus and bilaterally in the aMCC, pACC, and anterior insula. However, group differences in spatial extent and in subregions within a given region, were identified. For example, compared to controls, IBS subjects showed greater spatial extent of brain activity in regions of the B thalamus and B aMCC, regions associated with visceral afferent processing. Different insular regions were seen in IBS and control groups, with greater extension posteriorly to the mINS in IBS. IBS subjects showed thalamic activation in more medial regions, including the medial dorsal nucleus, while the control region was located caudally in the pulvinar nucleus. IBS showed greater consistent activity in the R pACC as well as L amygdala, regions associated with emotional arousal. IBS subjects had greater consistent activity of the R superior frontal cortex (BA 6) and of the midbrain, as noted in the within group analysis.

Healthy controls showed greater consistent activity in some aspects of the B aINS, the pulvinar thalamus, the putamen, and post/precentral gyrus (BA 43, S2). BA 40, a region involved in stimulus driven somatosensory attentional processing, was seen in controls, but not IBS.[38] In addition, the prefrontal cortex (L BA 9/46, R BA 9/32) was reliably activated in controls but not IBS subjects.

Discussion

The current ALE meta-analysis of supraliminal rectal inflation confirms the involvement of brain regions involved in visceral sensation, emotion arousal and attentional processes in both controls and IBS. Furthermore, the use of ALE techniques has allowed extension of these within group analyses to an IBS versus controls comparison showing group differences, particularly that IBS patients reliably engage known emotional arousal circuitry (amygdala, pACC) but healthy control subjects did not. The disparate results described in early studies of the brain's response to visceral stimulation led some to raise a concern about the reliability and validity of the methodology in studying brain responses to lower intestinal distension. However, those inconsistent results appear to be primarily the result of different a priori choices, study designs and analytical methods, rather than an intrinsic limitation of the investigational approach. As hypothesized, IBS subjects undergoing lower intestinal stimulation showed a greater extent of brain activity than controls, specifically in regions associated with visceral afferent processing and emotional arousal. While the traditional identification of the individual brain regions involved in response to visceral stimulation has been important, in order to gain a fuller understanding of these regions in the pathophysiology of IBS, it is important to view them in the context of the brain networks in which they are involved. Advances in the past few years have informed our understanding of the networks involved in both visceral sensation (*homeostatic afferent network*) and the associated emotional response (*emotional arousal network*). The *homeostatic afferent network* is comprised of the thalamus, insula and aMCC. [39] This network encompasses the sensory input entering the thalamus from the brainstem, with projections to the primary interoceptive cortex (posterior INS), and to the aMCC, which mediates affective, motivational and motor aspects of the stimulus. [20, 40, 41] The *emotional arousal network* (including the locus coeruleus complex, amygdala, hypothalamus, parahippocampal gyrus, pACC, aINS, and orbitofrontal cortex) is engaged in the emotional processes modulating visceral responses such as anticipatory anxiety or fear [9, 42, 43]. In the discussion of the results, we will focus on how the consistently involved brain regions described in the meta-analysis may operate within these functional networks. We will first discuss regions seen in both groups, and then discuss the observed group differences.

Brain regions engaged in both controls and IBS

Consistent with previous reviews, both control and IBS subjects showed activation of the thalamus, insula, and aMCC, though the specific regions seen in each group only partially overlap. These regions are key nodes within the *homeostatic afferent network*, as described by Mayer and colleagues. [39] Cortical regions associated with attentional processes were noted in both groups, though the specific location differed (BA 40 in control, BA 6 in IBS). Careful examination of attentional networks in IBS is lacking. The literature on attention suggests a role for BA 40 in the alerting response, as well as somatosensory attentional processing. [38, 44, 45] Brodmann area 6 is implicated in orienting to a stimulus and executive attention [44, 46] Just as limitations in study design preclude the differentiation between nociceptive and non-nociceptive aspects of ACC activation, control for attention was not a feature of most of the included paradigms, obviating a more specific interpretation.

IBS and control subjects also shared activation in the putamen, though the regions had no overlap in the conjunction analysis. While often noted as activated in visceral distension, the role of the putamen in these studies is largely unknown.

Brain regions showing greater engagement in IBS

Emotional arousal network—The most striking finding in comparison of IBS to controls was the greater engagement of specific nodes of the emotional arousal network

(amygdala, pACC). Neither of these regions showed foci with greater consistent activity in controls. Additionally, activation of medial prefrontal cortex, a brain region known to negatively modulate emotional arousal was not seen in IBS. [47–49] The greater engagement of the emotional arousal network is consistent with a model of IBS characterized by increased anxiety, vigilance and altered autonomic responses.[2] It has previously been suggested that greater engagement of emotional arousal circuitry may also play a role in central pain amplification.[50, 51] A factor not accounted for in this type of analysis is the time course of network activation. Individual studies have suggested that in IBS subjects, regions of the emotional arousal network may be preferentially activated by the anticipation of visceral pain, and that greater engagement during anticipation of visceral pain may be seen primarily in female patients.[9] It can be assumed that unless specific study paradigms were designed to differentiate brain responses to anticipation from the actual stimulus, brain responses during distension would be influenced by the anticipation response.

Homeostatic afferent network—IBS subjects also showed differential activation of regions in the homeostatic afferent network. Medial thalamic regions, including the medial dorsal nucleus, were seen with greater consistency in IBS. These thalamic nuclei have connectivity with the anterior cingulate and prefrontal cortices, consistent with stronger association of the afferent input to affective and motivation processing. [39, 52, 53] In comparison, the control subjects show posterior thalamic activity, in the pulvinar nucleus. Activation was seen across the groups in the insula, however the IBS groups shows great extension posteriorly into the mid-insula. A greater consistency of activation in the aMCC was seen in IBS compared to controls. This anterior region of the MCC is recognized to be activated by noxious visceral stimulation[44, 45] though in a review examining its role in emotional processing, its most anterior portion has been associated with fearful emotion.[45] Furthermore, more anterior activation of MCC extending into the superior portion of the pACC has been reported in studies of non-nociceptive pain, e.g. anticipated, imagined or empathy- related pain.[43] Since the majority of the published studies were not designed to distinguish between the response to the visceral distension and the anticipation of such stimulation, a conclusion as to whether these subtle differences in the location and extent of regions may represent functional differences in network activity cannot be determined from the current analysis.

IBS subjects show consistent activation of a large region of the midbrain across studies, while no reliable midbrain regions are seen in the controls. None of the studies included in this analysis used a specific protocol for brainstem imaging, thus determination of which specific nuclei are included in this region is not feasible. Additionally, the ALE process leads to aggregation of multiple small adjacent regions, which may include the PAG, nucleus cuneformis, and the red nucleus. These regions, all of which are involved in emotional and pain modulatory functions, have been reported previously in studies imaging nociception.[7, 54, 5556] The nucleus cuneformis and PAG have both been implicated in descending pain facilitation as well as inhibition.[57, 58] Greater descending pain facilitation or defects in descending inhibition may be mechanisms contributing to “central pain amplification”, e.g. the increased perceptual response to experimental and possibly physiological gut stimuli. Berman et al. (2008) described anticipation and distension related alterations in similar dorsal brain stem regions in IBS subjects, and specifically showed a lack of inhibition during anticipation, and greater activation during a painful stimulus.[7] Clearly, nuclei in this region play important roles in perceptual responses and possibly in symptom generation. Imaging protocols optimized to study this brain region are required.

Brain regions and networks showing greater engagement in controls

Controls show greater reliable activation primarily in cortical regions involved in modulation of pain and emotion as well as attention, including lateral PFC, medial PFC and BA 40.[48, 49, 59] The left lateral prefrontal cortex has been described in the cognitive control of emotion via reappraisal, and decreased activation of this region has been noted in women, in whom functional disorders are predominately seen. [60, 61] These findings are consistent with more effective down regulation of emotional arousal circuitry in controls, appropriate to the anticipation and sensation of an uncomfortable but tolerable visceral stimulus.

Limitations

This meta-analysis was limited by the availability of within group activation analyses from several previously published studies of lower gastrointestinal stimulation. However, it remains the only analysis of its kind in lower gastrointestinal distension and this quantitative meta-analytic approach significantly improves on the previously published systematic reviews. The individual studies analyzed included a variety of different stimulation paradigms and protocols, so by its nature this analysis displays mainly the most consistent and robustly activated regions involved in response to lower gastrointestinal stimulation. This approach may overlook regional activations or group differences specific to particular protocols. For example, previous studies have emphasized the importance of anticipation of visceral stimuli as an essential difference between IBS and control subjects and this analysis cannot differentiate between specific aspects of the experimental stimuli.[7, 33, 35]

Inhomogeneity in the patient populations of imaging studies of visceral sensation has been considered a barrier to interpretation [13] The analysis presented does not take into account bowel habit or sex, but despite this limitation, significant group differences are seen, suggesting at least some component of the central dysfunction in IBS are common across these sub-groups. This is consistent with the commonality of the cardinal symptoms (pain and discomfort) and frequently seen risk factors (psychological symptoms, early life trauma, co-morbid pain syndromes) seen in both gastrointestinal and non-gastrointestinal functional disorders. This meta-analysis cannot explicitly control for the presence of concomitant psychiatric or pain related disorders, or for the role of increased symptoms of anxiety or depression. Since the majority of studies did not control for such factors by rigorous patient selection (e.g. use of structured psychiatric interviews), it remains to be determined if the finding of greater engagement of emotional arousal circuitry is an essential component of IBS pathophysiology, or related to such comorbidity.

Previous reviews of the visceral stimulation imaging literature have noted within and between group differences in the somatosensory cortices, which we did not observe in the current analysis.[10, 11] Part of this discrepancy can be accounted for by the fact that S1 and S2 are more robustly activated by upper compared to lower gastrointestinal stimulation and to create a more coherent analysis, we included only lower GI stimulation. Also, the inclusion of later studies, which were more likely to include specific coordinates, and the fact that some fMRI studies may have failed to include S1 and S2 due to a limited field of view may also have contributed to this difference.

CONCLUSIONS

The interpretation of combined neuroimaging and visceral stimulation studies has long been limited by relatively small sample sizes and diverse study designs. This analysis allows, for the first time, a quantitative meta-analysis of the rich existing dataset with an empirical approach. As expected, we show reliable activation of homeostatic afferent regions in both IBS and control subjects, but with greater extent in the IBS group. Patients with IBS have

greater engagement of regions involved in emotional arousal network. These results support the role of central nervous system, IBS-control differences and most importantly, they will allow for more carefully designed experimental paradigms, to explore those networks which appear to best differentiate the central alterations in IBS responses to visceral stimulation.

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Abbreviations

ALE	Activation Likelihood Estimate
a	anterior
B	bilateral
BA	Brodmann area
fMRI	functional magnetic resonance imaging
control	healthy control
INS	\ insula
IBS	irritable bowel syndrome
MCC	midcingulate cortex
PAG	periaqueductal gray
pACC	perigenual anterior cingulate gyrus
PET	positron emission tomography
SMA	supplementary motor area

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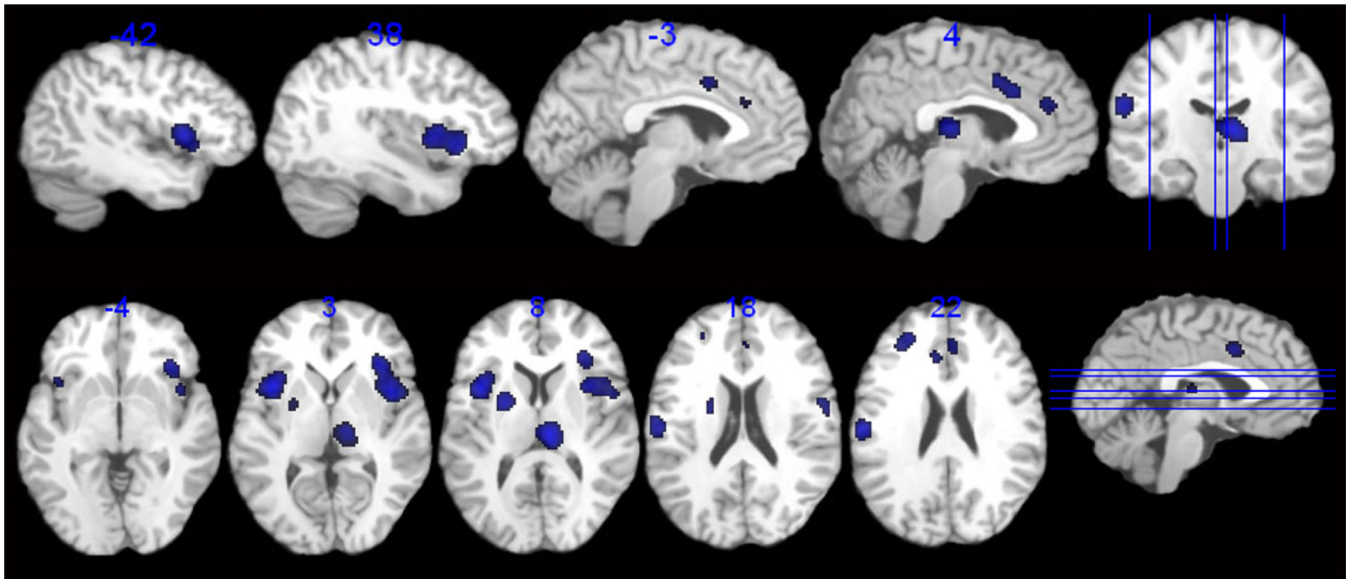

Figure 1.
Regions showing consistent and reliable activation across all studies in healthy controls.

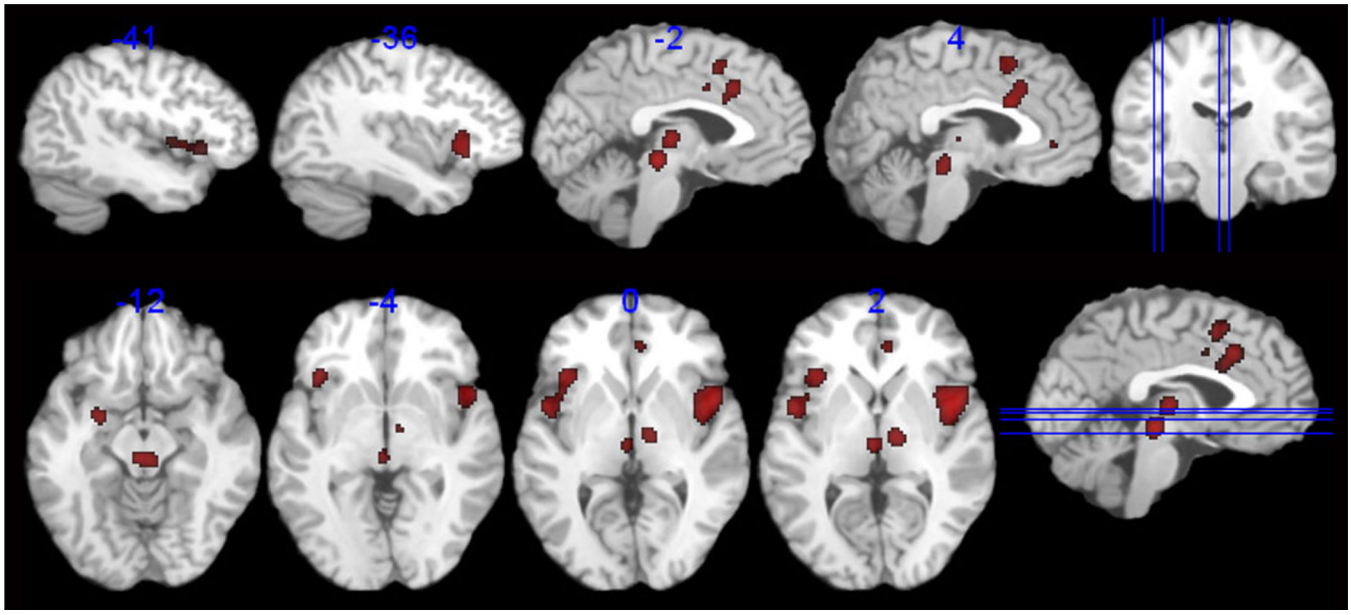

Figure 2.
Regions showing consistent and reliable activation across all studies in IBS patients.

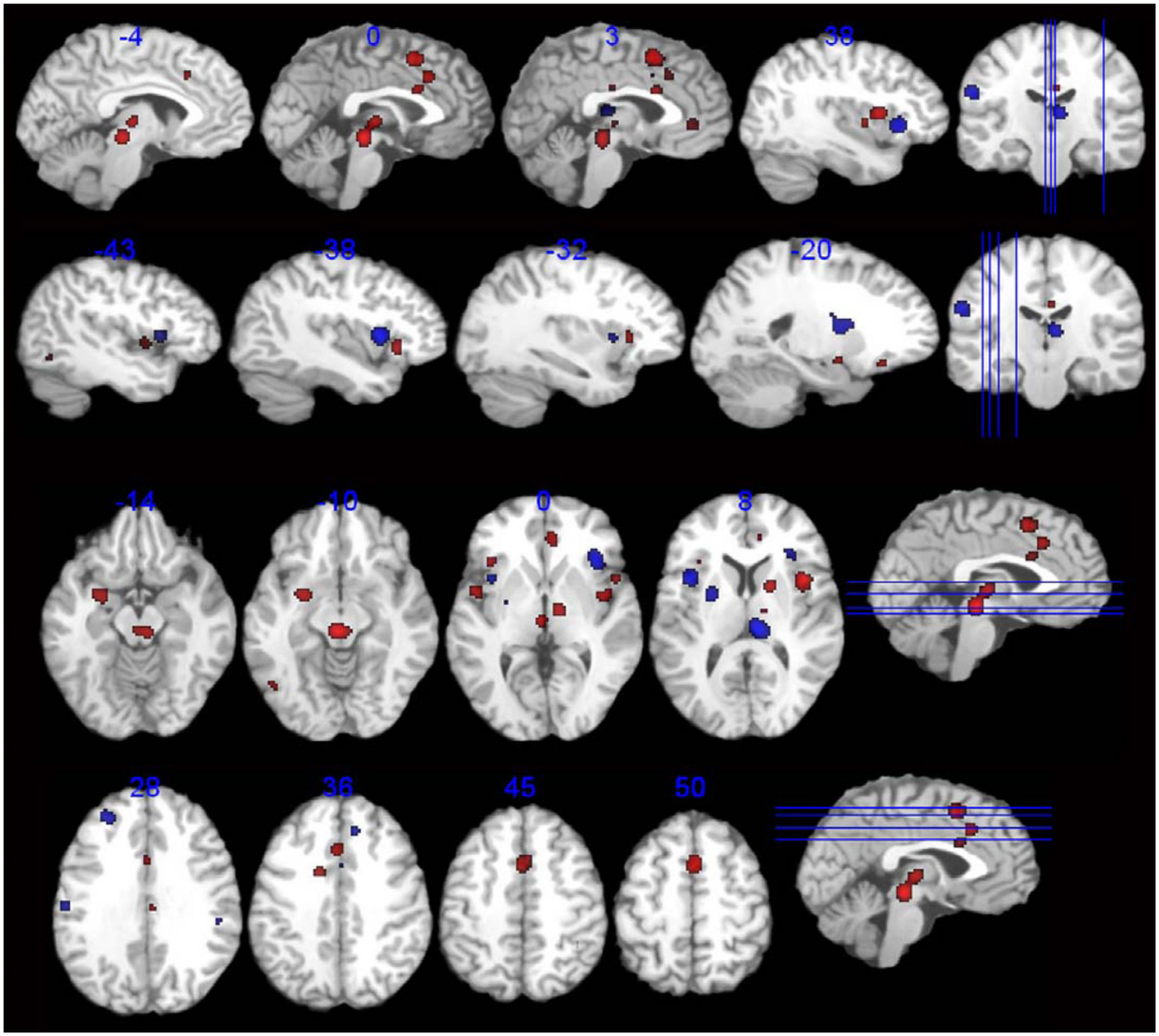

Figure 3.
Selected axial and sagittal slices representing brain areas demonstrating difference greater activation in IBS (red) and greater activation in Controls (blue) across all studies.

Table 1

Studies included in the meta-analysis

Study	Modality	Subjects	Supraliminal rectal inflation conditions
Berman et al. (2000)[23]	PET	Study 1: 13 (7 F) IBS	20, 45 and 60 mmHg
		Study 2: 17 (6 F) IBS	
Hobday et al (2001)[27]	fMRI	8 M Controls	average 11 p.s.i.
Lotze et al (2001)[30]	fMRI	8 Controls (4 F)	average 173.6ml
Naliboff et al (2001)[13]	PET	12 (2 F) IBS	45 mmHg
		12 (2 F) Controls	
Bonaz et al (2002)[25]	fMRI	11 (10 F) IBS	individually determined maximum tolerable volume
Verne et al (2003)[36]	fMRI	9 (6 F) IBS	55 mmHg
		9 (6 F) Controls	
Naliboff et al (2003)[32]	PET	42 (23 F) IBS	45 mmHg
Andresen et al (2005)[22]	fMRI	8 (3 F) Controls	individually determined perception threshold +10 mmHg
		8 (5 F) IBS	
Kwan et al (2005)[29]	fMRI	11 (7 F) Controls	individually determined moderate pain
		9 (6 F) IBS	
Berman et al (2006)[24]	fMRI	13 (6 F) Controls	25 and 45 mmHg
Naliboff et al (2006)[33]	PET	12 (8 F) IBS	45 and 60 mmHg
Song et al (2006)[35]	fMRI	12 F IBS	pain detection +20%
		12 F Controls	
Price et al (2007)[34]	fMRI	9 IBS	individually determined moderate pain (rating of 40 out of 100)
Berman et al (2008)[7]	fMRI	14 F IBS	25 and 45 mmHg
		12 F Controls	
Ringel et al (2008)[4]	fMRI	10 F Controls	15 and 50 mmHg
		10 F IBS	
Elsenbruch et al (2009)[26]	fMRI	15 F IBS	individually determined discomfort level
		12 F Controls	
Kanazawa et al (2010)[28]	PET	32 M Controls	20 and 40 mmHg
Moisset et al (2010)[31]	fMRI	11 F Controls	individually determined non-painful sensation and moderate pain
		M: Male; F: Female	

Table 2

Controls

Brain regions consistently activated and exceeding a false discovery rate threshold of p=.05 during supraliminal rectal balloon inflation in healthy controls.

Label	Cluster #	Volume (mm3)	ALE Value	Hemisphere	x	y	z	Studies Contributing
aINS	1	5752	0.0025	R	42	6	2	7, 13, 24, 26–31, 35, 36
aINS			0.0024		36	22	0	
Post central gyrus (BA 43)			0.0013		58	−8	16	
aINS	2	2968	0.0029	L	−38	8	6	7, 22, 24, 29, 30, 36
Thalamus	3	2256	0.0027	R	8	−24	8	13, 28, 29, 31, 36
Inferior parietal lobule (BA 40)	4	1744	0.0023	L	−56	−20	22	22, 27, 29, 30, 35
Putamen	5	1680	0.0025	L	−22	0	12	28,31,13,,35
aMCC (BA 24)	6	1320	0.0018	R	6	16	30	22, 24, 27, 29
			0.0017	L	0	6	36	
Lateral prefrontal cortex (BA 9/46)	7	1088	0.0019	L	−26	40	24	13, 29, 35
Inferior parietal lobule (BA 40)	8	408	0.0018	R	52	−30	30	28, 31
pACC (BA 32)	9	296	0.0013	R	4	36	22	22, 24
aMCC/pACC (BA 32)	10	272	0.0013	L	−6	28	24	24, 36
Medial prefrontal cortex (BA 9/32)	11	168	0.0013	R	12	32	34	13, 31

Table 3

IBS

Brain regions consistently activated and exceeding a false discovery rate of p=.05 during supraliminal rectal balloon inflation in IBS patients.

Region	Cluster #	Hemisphere	Volume (mm3)	ALE Value	x	y	z	Studies Contributing
a/mINS	1	R	4304	0.0034	40	8	6	7, 13, 22, 23, 26, 29, 32–35
Superior temporal gyrus (BA 22)	2	L	1960	0.0020	−48	2	2	7, 26, 29, 32, 35, 36
aINS				0.0021	−34	20	4	
aMCC (BA 32)	3	L	1288	0.0021	0	18	34	7, 13, 33
aMCC (BA 24)		R		0.0021	2	12	28	
Midbrain	4	L	1072	0.0025	0	−28	−8	7, 32, 33
Cerebellum		R		0.0020	6	−30	14	
Thalamus	5	R	960	0.0025	12	−16	6	13, 22, 32, 36
Superior frontal gyrus (BA 6)	6	R	704	0.0019	2	10	48	22, 34, 35
Thalamus	7	L	496	0.0021	−2	−20	4	29, 33
a/pMCC (BA 24)	8	L	312	0.0014	−10	4	36	7, 32
Amygdala	9	L	264	0.0018	−24	−4	12	23, 32
pACC (BA 24)	10	R	192	0.0014	6	36	2	7, 32
Putamen	11	R	112	0.0015	18	4	6	29, 36

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Table 4

GROUP DIFFERENCES

Consistent differences in brain regions activated activations during supraliminal rectal balloon inflation in IBS patients compared to controls.

IBS > HEALTHY CONTROL							
	Region	**Hemisphere**	**Volume mm^3**	**ALE Value**	**x**	**y**	**z**
1	Midbrain	R/L	1704	0.0173	0	−28	−8
	Thalamus (medial dorsal nucleus)	L		0.0131	−2	−20	2
2	Thalamus	R	1672	0.0150	10	−14	0
3	mINS	R	1256	0.0161	40	8	8
4	SMA (BA 6)	R	920	0.0153	2	8	48
5	Amygdala	L	536	0.0123	−24	−4	−12
6	pACC (BA 24)	R	472	0.0107	6	36	2
7	Putamen	R	400	0.0128	18	4	6
8	aINS	L	368	0.0104	−36	20	0
9	aMCC (BA 32)	R	328	0.0112	0	18	36
10	aINS	L	312	0.0114	−46	0	0
11	aMCC (BA 24)	L	288	0.0103	−14	4	34
12	aMCC (BA 24)	R	240	0.0109	2	10	26
HEALTHY CONTROL >IBS							
	Region	**Hemisphere**	**Volume mm^3**	**ALE Value**	**x**	**y**	**z**
1	aINS	R	1344	−0.0107	36	22	0
2	Thalamus (pulvinar)	R	1312	−0.0174	8	−26	8
3	Putamen	L	1080	−0.0134	−22	−2	12
4	aINS	L	968	−0.0173	−38	10	6
5	Dorsolateral prefrontal cortex (BA 9/46)	L	776	−0.0126	−26	42	26
6	Inferior parietal lobule (BA 40)	L	664	−0.0153	−56	−20	24
7	Pre/Post central gyrus (BA 43)	R	344	−0.0107	58	−8	14
8	Inferior parietal lobule (BA 40)	R	168	−0.0104	52	−30	30
9	Medial prefrontal cortex (BA 9/32)	R	144	−0.0095	12	32	34