Regional Gray Matter Density Changes in Brains of Patients with Irritable Bowel Syndrome

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Abstract

Background & Aims—Several studies have examined structural brain changes associated with chronic pain syndromes, including irritable bowel syndrome (IBS), but study sample sizes have been small and heterogeneous.

Methods—We used magnetic resonance imaging (MRI)-based techniques, voxel-based morphometry, and cortical thickness analysis, to examine brain anatomical differences in a relatively large, tightly screened sample of IBS patients (n=55); we compared data with that from healthy individuals (controls, n=48).

Results—IBS was associated with decreased gray matter density (GMD) in widespread areas of the brain, including medial prefrontal and ventrolateral prefrontal cortex, posterior parietal cortex, ventral striatum, and thalamus. Compared with controls, we observed increased GMD in patients with IBS in the pregenual anterior cingulate cortex and the orbitofrontal cortex, as well as trends in the posterior insula/secondary somatosensory cortex, (para)hippocampus, and left dorsolateral prefrontal cortex. In accounting for anxiety and depression, we found that several of the regions involved in affective processing no longer differed between patients with IBS and controls, whereas the differences in prefrontal and posterior parietal cortices remained. The areas of decreased GMD associated with IBS were largely consistent across clinical subgroups, based on predominant bowel habit and pain predominance of symptoms. There were no overall or regional differences in cortical thickness between patients with IBS and controls.

Conclusions—Changes in density of gray matter among regions involved in cognitive/evaluative functions are specifically observed in patients with IBS, whereas changes in other areas of the brain can be accounted for explained by levels of anxiety and depression.

Keywords

neuroimaging; VBM; neural; visceral

Introduction

Irritable bowel syndrome (IBS) is a complex, symptom-based disorder defined by recurrent abdominal pain or discomfort associated with alterations in bowel habits[1]. The syndrome is heterogeneous, with subgroups based on predominant bowel habits, and most bothersome symptoms. Increased anxiety (or anxiety disorders) is observed in the majority of patients[2]. As would be predicted with such a heterogeneous syndrome, results of functional neuro-imaging studies in IBS patients show variable results; nevertheless, increased regional activity in insula (INS) and anterior midcingulate cortex (aMCC) have been most commonly reported[3].

IBS has been categorized as a "functional" pain syndrome, along with a number of other syndromes that have as a characteristic pain of unknown origin, including fibromyalgia, chronic low back pain, headache, and chronic vulvar pain. Although increased afferent drive may contribute to the hypersensitivity of these syndromes, accumulating evidence suggests that an alteration in descending pain modulation, and an associated alteration in cortico-limbic-pontine brain circuits may make an important contribution to the hypersensitivity[4]. Structural abnormalities in these regions have been identified in small populations of patients suffering from different persistent pain disorders (including fibromyalgia[5-8], chronic low back pain[9, 10], and headache/migraine[11-13] and chronic vulvar pain[14]). Although decreases in gray matter size predominate, in some cases, increases in regional gray matter are observed and interpreted as a possible use-dependent hypertrophy[14]. The relationship of changes in gray matter density (GMD) with functional alterations and symptoms in pain disorders, and the underlying mechanisms remain incompletely understood. Regional GMD changes may be a trait of patients or could be consequence of disease through mechanisms such as neurotoxicity or neuroinflammation (in the case of GMD decreases) or from use-related increases [15-18]. Two studies have also reported morphometric differences between small samples of IBS patients and healthy controls, which included a reduction in GMD and cortical thickness (CT) in aMCC [19, 20]. However, these studies did not determine which characteristics of IBS patients (e.g., pain, other IBS symptoms, anxiety, depression) contributed to the anatomical abnormalities.

In the current study, we attempted to dissect possible components of neuro-anatomical abnormalities in IBS patients by evaluating a large tightly screened sample of female IBS patients, for which we had information about multiple IBS symptoms, as well as measures of anxiety and depression. We hypothesized that: 1) IBS is associated with decreased gray matter in regions shown to have increased responsiveness to rectal distension and its expectation, including INS and ACC, possibly due to over-use excitotoxicity; 2) IBS is associated with an increase in gray matter in some regions, particularly in regions involved in cognitive and attentional modulation of interoceptive information, consistent with a role of these regions in central pain amplification; 3) depression, anxiety, and predominant symptom explain part of the anatomical differences between IBS and controls.

Materials and Methods

Subjects

The sample consisted of 106 women of whom 56 had IBS and 49 were age matched female controls from 3 different fMRI study protocols performed on the same MRI scanner. These studies were approved by the Office for the Protection of Research Subjects at the University of California, Los Angeles. Subjects for these studies were recruited by advertisement and from specialty clinics of the UCLA Division of Digestive Diseases. All patients were evaluated by 1 of 2 gastroenterologists at the UCLA Center for Neurobiology of Stress, experienced in the diagnosis of functional gastrointestinal disorders. IBS patients met ROME II criteria and were screened by a psychologist using a structured psychiatric interview (SCID) to exclude any patient with a recent DSM IV diagnosis of mood and affect disorders. Patients were also excluded if they were taking any centrally acting medications, such as antidepressants (TCAs, SSRIs, NSRIs), anxiolytics, or pain medications. Three subjects were excluded due to missing behavioural data (n=2) and poor MRI data (n=1).

Questionnaires

Each subjects completed the Brief Symptom Inventory (BSI[21]), the Hospital Anxiety and Depression Scale (HADS[22]) and the UCLA Digestive Disease Center Symptom Questionnaire (BIS[23]), and reported his or her most bothersome symptom and bowel habits (constipation, diarrhea, or alternating). Symptom severity was assessed on a 5-point scale from 0. None: no symptoms to 4. Very severe: markedly affects my lifestyle.

MRI

Brain images were acquired on a 3T MRI scanner (Siemens Allegra). First, a sagittal scout was used to position the head. Then each subject underwent a high-resolution 3D T1-weighted, sagittal, magnetization prepared rapid gradient echo (MPRAGE) [TR = 2.3ms, TE = 0.00285ms, flip angle 9, final resolution 1×1×1mm].

VBM and CTA preprocessing

We used the CIVET pipeline (v. 1.1.9) for all preprocessing of VBM and CTA data (http://wiki.bic.mni.mcgill.ca/index.php/CIVET). Details (including references) of these methods are provided in Supplementary Methods. For VBM, tissues were classified as gray matter (GM), white matter (WM), or CSF, and smoothed 8mm. Cortical thickness in mm was calculated at 81924 vertices for each brain and smoothed 20mm. Cerebellum was excluded from analyses.

Analysis

For whole brain tissue analyses, we extracted the mean gray matter density (GMD), white matter density (WMD), and CSF density, as well at the mean cortical thickness for each individual. We plotted these values against age and performed a one-way ANOVA to compare between groups (SPSS 16.0, SPSS Inc.).

We used SurfStat (http://www.stat.uchicago.edu/~worsley/surfstat/) for VBM and CTA. We applied a general linear model (GLM) comparing groups, with age as a covariate of no interest. Separate GLMs comparing controls and IBS were run for CTA and VBM with the covariates: age; age + anxiety; age + depression; age + anxiety + depression. In addition for VBM, we performed separate analyses comparing subgroups of IBS patients with age as a covariate. The subgroups were based on bowel habits (constipation (n=15), diarrhea (n=17), alternating (n=19), or unspecified (n=5), or whether the most bothersome symptom was pain (pain predominant, n=17) or something else (non-pain predominant, n=38). However, all patients

reported abdominal pain as one of their symptoms, and met the Rome II criteria[24]. For all analyses, corrections for multiple comparisons were performed using random field theory-based cluster analysis[25]. We set a threshold so that only contiguous voxels with a t-value of greater than 2.5 could be considered in the cluster analysis. Results from the GLM analyses are thus reported as corrected at the cluster level. For the CTA, we ran a threshold of threshold set at p<0.05 for the voxels to be included in the cluster analysis.

For brain regions known to process nociceptive information and interoception, including primary (S1) and secondary (S2) somatosensory cortices, INS, ACC, and PFC, brainstem, and thalamus, regions which are also most commonly observed to have different GMD between controls and chronic pain populations (e.g.[14]), we applied a liberal corrected threshold (p<0.1; note that the cluster contains voxels showing a minimum t-value of 2.5, so the uncorrected threshold at the voxel level is about p<0.01).

For each significant cluster from the GLM analysis between IBS and control groups removing age, we extracted the mean GMD for each subject for plotting results, and for the analyses below.

To compare the pain predominant (n=17) and non-pain predominant (n=38) groups, we computed GLMs between groups with age as a covariate for the average GMD in each significant cluster in the overall group comparison between IBS and controls.

To test for effects of disease duration and symptom severity, we performed bivariate correlation analyses between each of the variables IBS duration and IBS symptom severity and the GMD each significant cluster from the GLM analysis between IBS and control groups removing age.

Results

Patient characteristics

Subject characteristics (age) and behavioural variables (depression and anxiety) for IBS and controls are shown in Table 1. Mean ages (SD, range) for IBS and controls were 31.0 (12.3, 19-57) and 32.2 (10.1, 19-63), respectively. Of those 39 controls and 53 IBS who provided menses stage information, 5 controls and 4 IBS were postmenopausal. Patients had a wide range of disease duration (11.1+7.7, median 9.0; range: 1 to 34 years) and moderate IBS symptom severity (2.0+0.5, median 2.0; range 1 to 3 on a scale from 0 to 4).

Although IBS had statistically significantly higher anxiety (5.9+3.5 vs 3.5+2.4; on a scale from 0- 21; p<0.001) and depression scores (3.0+2.8 vs 0.8+0.9; on a scale from 0 - 21; p<0.001) than controls, both individual values and means for both groups were at subclinical levels for anxiety and depression. Further characteristics of the sample subgroups are given in Table 1.

Whole brain tissue densities

Regardless of group, we found age-related decreases in overall GMD and cortical thickness, and age-related increases in CSF, as expected (Figure 1). No significant differences between groups were seen for these whole brain age-related changes (one-way ANOVA, p>0.5 for each tissue type).

VBM

VBM results are summarized in Figures 2 and Table 2. Both decreases and increases in GMD in the IBS group compared to controls were observed.

Decreased GMD in IBS—The group GLM with age as a covariate of no interest revealed decreased GMD clusters in IBS relative to controls in left posterior parietal cortex (PPC; BA 40/7) and precuneus, bilateral temporal lobe (right ventral temporal pole, left middle and inferior temporal gyri); bilateral vlPFC (BA 10) and medial PFC (mPFC, BA 10), left middle frontal gyrus (MFG, BA 46), bilateral thalamus/midbrain (this cluster consisted primarily of bilateral ventral medial thalamus, which extended ventrally to posterior medial midbrain (which contains the periaqueductal gray (PAG)), bilateral ventral striatum, premotor cortex (BA 6), and a small cluster in occipital cortex.

Increased GMD in IBS—Clusters with greater GMD in IBS than controls included midline pregenual ACC (pACC, BA 24/32) and left orbitofrontal cortex (OFC, BA 11). At a lower threshold (p<0.1 corrected), other areas with increased GMD included bilateral hippocampus/parahippocampus (Hc/pHc), right S2/posterior insula cortex (S2/pINS), and left dlPFC (BA 9). The increased S2/pINS and Hc/pHc GMD are shown in Supplementary Figure 1 as T-maps masked by clusters.

Covariate with anxiety and depression—Results of analyses that included the addition of anxiety, depression, or anxiety and depression as covariates (along with age in each case) for IBS versus controls, are summarized in Table 2. Inclusion of either anxiety or depression as covariates abolished the group differences in bilateral ventral striatum, and left OFC. Inclusion of anxiety and depression together as covariates additionally removed the group differences in bilateral thalamus/midbrain and left pACC. However, even after controlling for depression and anxiety, group effects between IBS and controls remained in left PPC, bilateral temporal cortices, and left MFG.

IBS symptom based subgroups—Comparing pain predominant (n = 17) and non-pain predominant groups demonstrated lower GMD in the pain predominant subgroup ($F_{1,32} = 7.11$, p=0.010) in the dlPFC cluster that was found to have greater GMD in IBS than controls. A comparison of the dlPFC decrease compared to controls in Figure 4 (far right column) indicates that only the non-pain predominant group showed this GMD increase. Also shown in Figure 4 are areas of reduced GMD in all IBS compared with controls that are apparently driven by either the pain predominant group (vlPFC, vStr) or the non-pain predominant group (thalamus/midbrain, mPFC).

The results for GLM and cluster analyses for the subgroups of IBS subjects based on bowel habits are summarized in Table 2. Of note is that the IBS-C does not appear to contribute to the decrease in thalamic GMD relative to controls. In general, the findings of decreased or increased GMD relative to controls is consistent across all bowel habit subgroups, with the exception of the thalamus, the OFC, and pACC, regions in which the constipation-predominant group does not differ from controls.

We found only one significant (p<0.05, uncorrected) correlation between either IBS severity or IBS symptom duration and any of the average gray matter values for the clusters from the group (removing age) GLM. This was a small negative correlation between IBS duration and the dlPFC cluster GMD (r = -0.28, p<0.05). This correlation was found to only be in the non-pain predominant group (r = -0.35, p<0.05) and not in the pain group (r = -0.22, p=0.40).

CTA

We found no significant differences between groups regardless of the covariates entered.

Discussion

Here we report morphometric brain differences between IBS patients and controls, in terms of regional increases and decreases in gray matter density, while no differences in total gray matter density or cortical thickness were observed. Even though some similarities with previously published results from other patient populations were observed, many of the involved regions were different, and a number of regions with *increased* gray matter density were observed. Results from both cortical thickness and voxel-based morphometry analyses indicated that whole brain gray matter density and cortical thickness decreased in both IBS and controls with age, but there were no differences between groups. Highly significant regional differences were seen with voxel-based morphometry, but not with cortical thickness analysis.

Even though significant changes in gray matter density were observed in multiple regions, we limit our discussion to the regions implicated in our two main a priori hypotheses, and compare them to published results in the literature from patient populations with various persistent pain disorders.

Hypothesis 1. IBS is associated with decreased gray matter in regions shown to have increased responsiveness to rectal distension and its expectation

This hypothesis was based on the concept that morphometric changes observed in key regions of the so-called "pain matrix" in various patient populations with persistent visceral or somatic pain (including IBS) may be a consequence of chronic nociceptive input from the periphery[9, 11, 13, 26], possibly involving glutamate induced excitotoxicity, or other neurodegenerative processes. Increased visceral afferent signalling to the brain as a consequence of peripheral or central sensitization in IBS pathophysiology has been suggested, and some, but not all studies have shown that IBS patients indeed show greater activation in insula and cingulate cortices in response to an acute visceral stimulus[3], or to expectation of visceral stimuli[27]. However, in the current study, there was no significant gray matter density reduction observed in either cingulate or insula cortices. Our results are in contrast to findings of Davis and colleagues in a smaller sample of IBS patients[19], which included decreased cortical thickness in right anterior midcingulate cortex and bilateral anterior insula, and decreased gray matter density in aMCC and thalamus. In a recent study of a different sample, the same group reported cortical thinning in the aMCC. In the aINS, cortical thickness was related to symptom duration, with thinning only seen in patients with short duration of symptoms[20]. In contrast, but similar to our findings, Schweinhardt et al. did not observe morphometric differences in insula and anterior cingulate cortex in a study of female patients with provoked vestibulodynia, a form of chronic vulvar pain[14]. They speculated that the absence of gray matter density reductions in these regions may have been unique to their study population, in which pain is not constant but only experienced during stimulation, e.g. during intercourse. In this sense lower abdominal pain in IBS is analogous to pain in provoked vestibulodynia, since it is not constant (in contrast to functional abdominal pain syndrome[28]) but only occurs in association with bowel movements and/or food intake.

In summary, we did not confirm our hypothesis of gray matter density decreases within the interoceptive network; in fact, we observed a non-significant increase (IBS>control) of gray matter density in right S2/posterior insula (Supplementary Figure 1). S2/pINS is considered the primary interoceptive cortex, and is activated during noxious and thermal stimulation[29]. Because of its role in interoceptive processing, individuals with increased pINS gray matter density may be more vulnerable to central amplification of normal interoceptive input. It should be noted that for these regions about which we had *a priori* hypotheses, we applied a lower statistical threshold. This increases the chance of type I statistical error, although our use of cluster analysis still gives us much confidence in the results.

Hypothesis 2. IBS is associated with an increase in gray matter in some regions, particularly in regions involved in cognitive and attentional modulation of interoceptive information

This hypothesis was based on the concept that regional gray matter density changes may be a genetically determined or acquired trait of IBS patients which is positively correlated with function of involved brain circuits. Evidence for such a positive correlation between cortical volume and function has been provided from different lines of investigation[18, 30]. Based on this hypothesis, gray matter density reductions would be expected to be associated with reduced functionality and vice versa.

We found gray matter density *reductions* in several prefrontal regions, in particular bilateral ventrolateral prefrontal cortex. The right vlPFC plays a role in cognitive modulation of pain[31], and in placebo analgesia[32]. Previous studies reported compromised engagement of right vlPFC in IBS patients[27, 33] and it is intriguing to speculate that reduced gray matter density in this area provides a neuroanatomical basis for compromised control of emotion and pain perception. In support of this hypothesis is our finding that VBM reduction in vlPFC was contributed exclusively by the subgroup of patients who identified pain as their most bothersome symptom (see below).

Similar to findings in several other populations of chronic pain sufferers[5, 26], we found reduced gray matter density in medial prefrontal cortex. mPFC activity has been associated with antihyperalgesia[34], and release of endogenous opioids in mPFC has been demonstrated during tonic pain[35]. The reduced gray matter density in mPFC might therefore be related to a reduced ability to engage this pain inhibition system. Inhibitory interactions between mPFC and dorsolateral prefrontal cortex have been reported, and an alteration in these interactions has been implicated in low back pain patients[36]. Decreases in dlPFC gray matter density have been reported in patients with low back pain[9], arthritic hip pain[37] and migraine[38]. We found a gray matter density increase in a small area of dlPFC in the patient group (in the non-pain predominant group), as well as decreased gray matter density in premotor cortex and middle frontal gyrus.

We also found highly significant *reductions* in thalamus/midbrain gray matter density (including periaqueductal gray), and which were independent of anxiety and depression symptoms. As the PAG plays a prominent role in descending pain modulation, and alterations in the engagement of endogenous pain modulation systems has been suggested as a possible mechanism contributing to central pain amplification in IBS[33, 39, 40], these gray matter density reductions in the PAG region may be related to compromised descending modulation of pain.

Hypothesis 3. Depression, anxiety, and predominant symptom explain part of the anatomical differences between IBS and controls

Emotional modulatory regions and the effects of depression and anxiety—
Emotional factors, in particular anxiety and increased stress responsiveness play an important role in the modulation of chronic pain[2, 41]. An increased prevalence of anxiety disorders and depression has been reported both in patients and in non-healthcare seeking individuals who meet symptom criteria for IBS[2]. We showed that controlling for anxiety and depression eliminated many of the regions considered to be part of an emotional arousal circuitry, including ventral striatum, medial thalamus/midbrain, mPFC, pregenual anterior cingulate cortex, and orbitofrontal cortex. In a previous study in IBS patients, the decreased gray matter density in the anterior/medial thalamus in IBS patients[19] may in fact have been related to subclinical levels of anxiety or depression.

Pain as the most bothersome symptom—In order to explore if morphometric brain changes in IBS may be related to clinical characteristics of these patients, we looked at

subgroups of patients based on symptom duration, IBS symptom severity, pain predominance (patients who described pain as the most bothersome of their symptoms), and bowel habits. Visceral sensitivity – which is not a constant trait of IBS patients and was only evaluated in a small subset of the current sample – was not used in these analyses. Only pain-predominant patients showed reductions in ventral prefrontal pain inhibitory regions (vlPFC), as well as in the ventral striatum. In contrast, those who identified a symptom other than pain as most bothersome, showed gray matter density reductions in dlPFC, mPFC and thalamus/midbrain, the latter including the PAG. Based on the implications of all these regions in different cortico-limbic-pontine modulatory systems[33, 36], we suggest that differential alterations in these systems may result in different predominant symptoms. However, this hypothesis will have to be tested in larger samples. The fact that no major correlations with symptom duration was observed, argues against the concept that prolonged altered signalling from the gut may induce secondary reductions in regional brain volumes. The question of whether the observed volumetric changes are related to primary alterations brain activity, or if they are a consequence of altered visceral signalling to the brain, could be addressed by studies looking at gray matter density changes in patients undergoing successful cognitive behavioural approaches, or in studies of asymptomatic relatives of IBS patients.

Conclusions—The findings in this large sample of female IBS patients with moderate symptom severity suggest that morphometric alterations occur primarily in brain networks concerned with attention and emotion modulation, as well as in cortio-limbic pontine pain modulatory systems, and to a smaller degree in networks processing interoceptive information (as suggested by the increased gray matter density of pINS). Future studies in much larger samples of patients are required to correlate cognitive (attention, hypervigilance, catastrophizing), affective (trait anxiety), and pain measures with the observed morphmetric brain changes. The finding that changes in the attentional and emotional networks as well as in the primary interoceptive cortex were not related to disease duration or severity suggests the possibility that these structural changes are endophenotypes of IBS, which may also be detectable in asymptomatic relatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

| Hc | hippocampus |
| pHc | parahippocampal gyrus |

IBS-C/D/A	irritable bowel syndrome (patient) – constipation/diarrhea/alternating
m/vl/dlPFC	medial/ventrolateral/dorsolateral prefrontal cortex
(p)ACC	(pregenual) anterior cingulate cortex
PPC	posterior parietal cortex
MFG	middle frontal gyrus
OFC	orbitofrontal cortex
S2/pINS	secondary somatosensory cortex/posterior insula
aINS	anterior insula
(a)MCC	(anterior) midcingulate cortex
VBM	voxel-based morphometry
GMD	gray matter density
CT(A)	cortical thickness (analysis)

Figure 1. Age-related brain changes
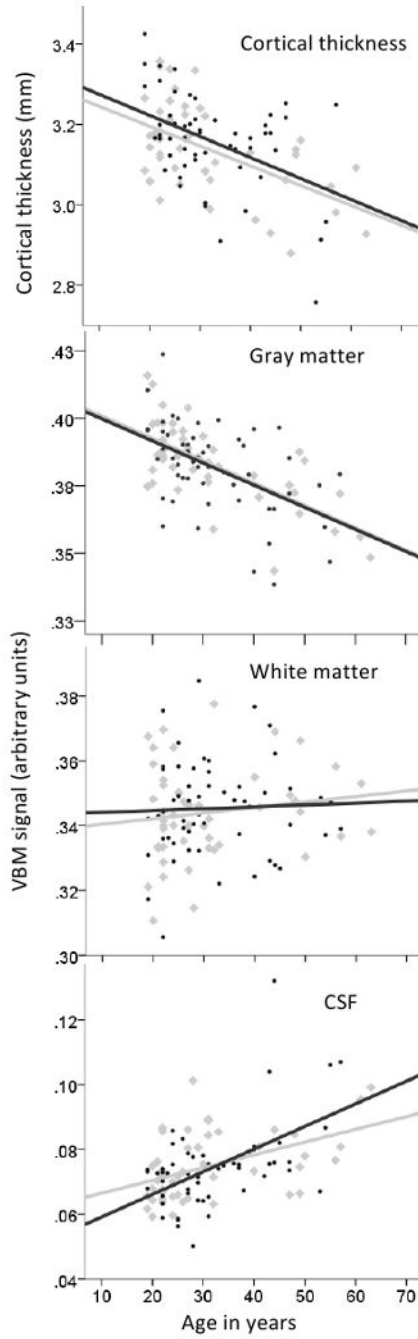Scatter plots for IBS (black symbols and regression lines) and healthy controls (gray symbols and regression lines) are shown for average cortical thickness (CT), gray matter density (GMD), white matter density, and cerebrospinal fluid (CSF) density across the whole brain. Age-related decreases in GMD and CT are as expected, with no apparent differences between IBS and controls.
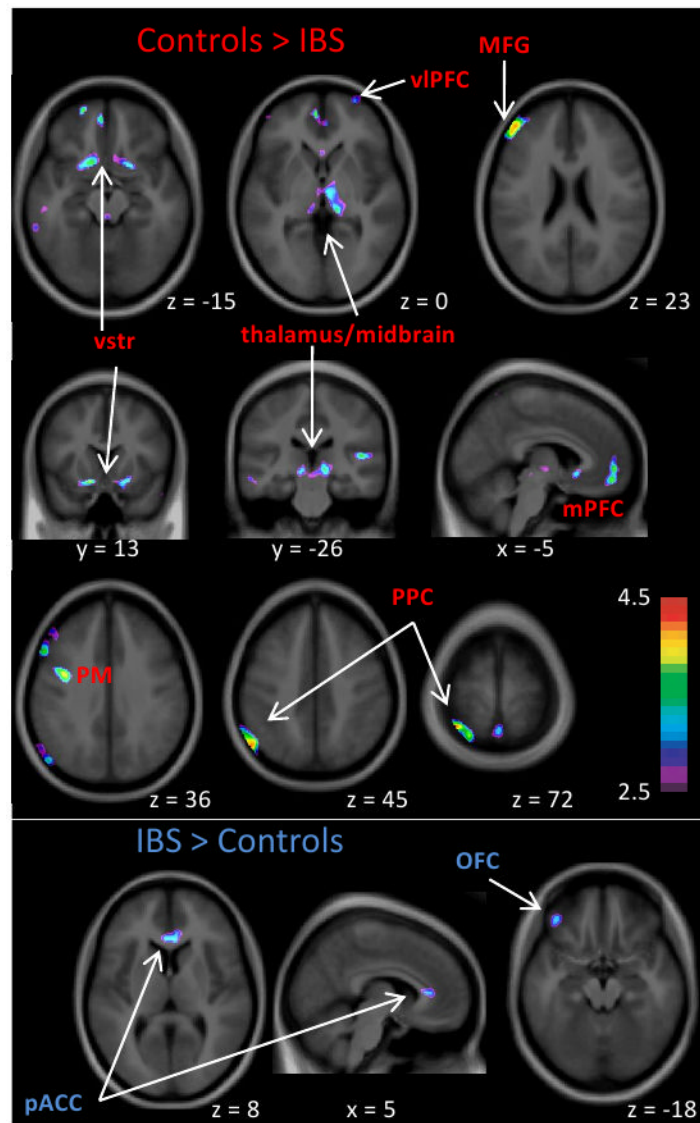
Figure 2. VBM results
Significant GMD clusters from GLM comparing IBS and controls, with age as a covariate.
Peak coordinates and correlations with behavioural variables are shown in Table 2. Results are
displayed on a group average brain in stereotaxic (MNI) space. See table 2 for abbreviations.
Colour bar shows t-value. Left side of image is left side of brain.
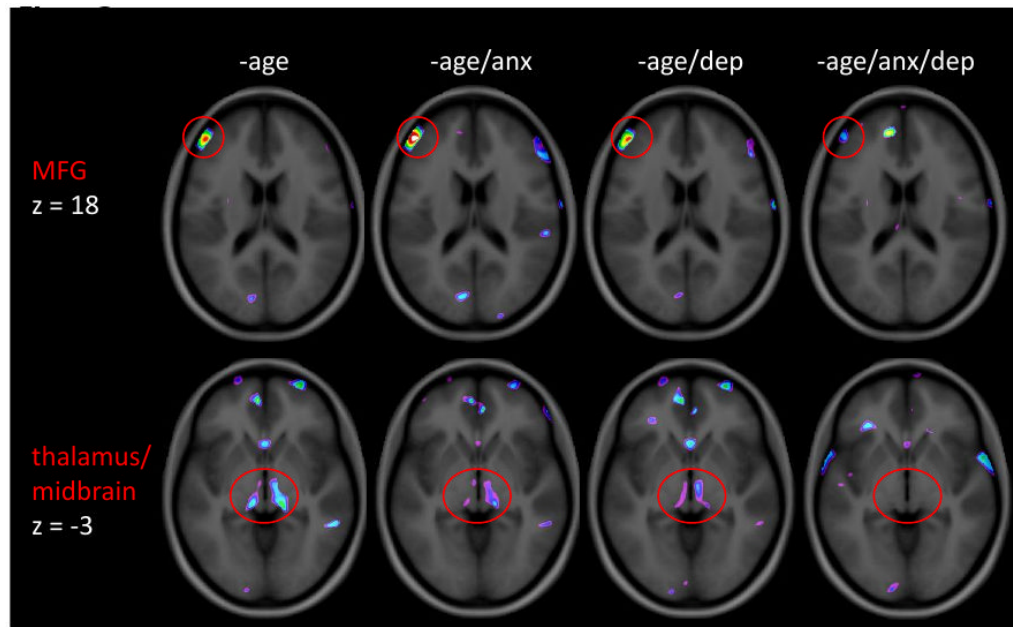
Figure 3. Covariates with anxiety and depression
Examples of regions affected by adding covariates anxiety and depression to the GLM. The vlPFC cluster shown on the top row was significant in all GLMs, regardless of the covariate (s). The bottom row compares the thalamus cluster, which is eliminated when anxiety and depression are included as covariates. The image is thresholded the same way as figure 2 (i.e. t>2.5 up to t=4.5). No masking has been applied to the images (i.e. whole brain results shown).
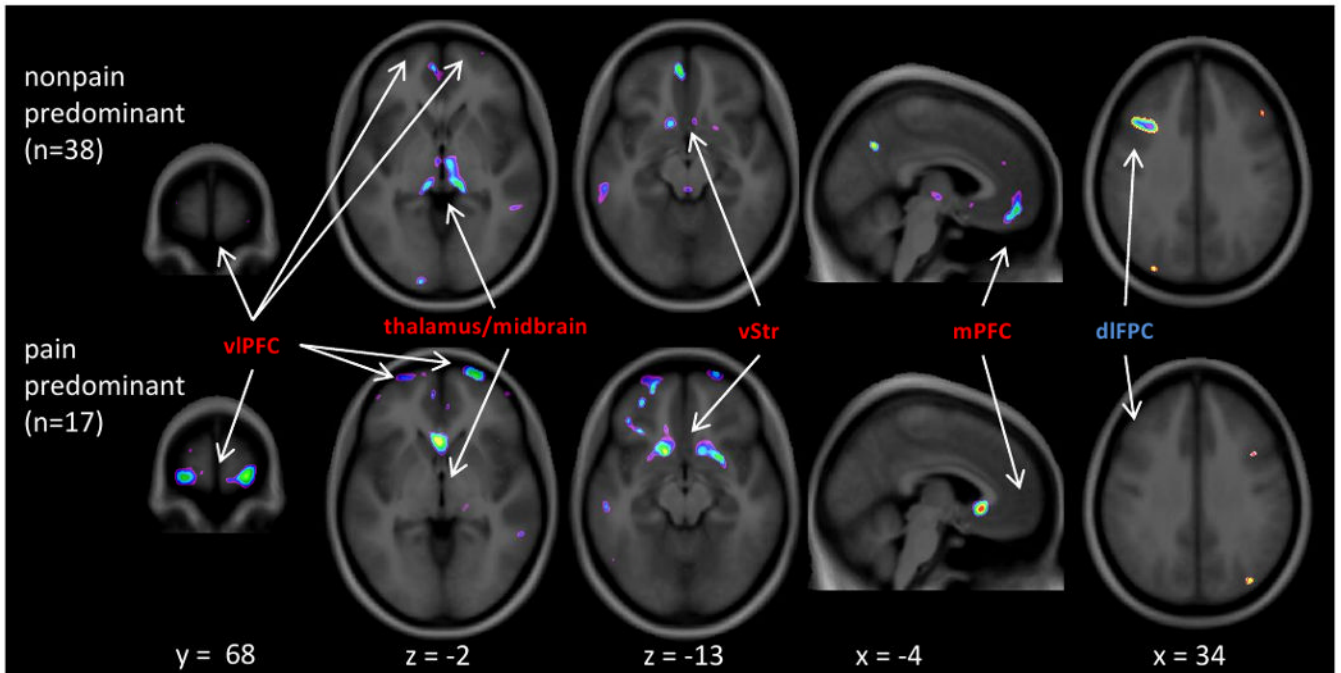
Figure 4. GMD differences between pain predominant and non-pain predominant groups
Examples of regions that differ between IBS subgroups based on most bothersome symptom (Pain, or Nonpain, which includes any other symptom). The clusters in red font are those that showed decreased GMD overall in IBS versus controls, whereas the blue is where IBS had increased GMD relative to controls. The figure clearly illustrates that the pain predominant group contributed the vlPFC and ventral striatum differences, while the non-pain predominant group contributed the differences in the thalamus/midbrain, mPFC, and dlPFC. The image is thresholded the same way as figures 2 and 3 (i.e. t>2.5 up to t=4.5). No masking has been applied to the images (i.e. whole brain results shown).

Table 1

Subject characteristics

Values are presented as mean (standard deviation). F- and p-values are from one-way ANOVA between IBS (n=55) and controls.

	IBS (n=55)	IBS-C (n=15)	IBS-D (n=17)	IBS-A (n=19)	Controls (n=48)	F-value (p-value)
Age	32.2 (12.3)	35.0 (13.4)	32.0 (5.46)	31.2 (10.9)	31.1 (12.3)	0.243 (0.62)
Anxiety[¥]	5.89 (3.50)	6.67 (3.67)	5.24 (2.68)	5.21 (3.16)	3.49 (2.38)	16.5 (<0.0001)
Depression[¥]	2.98 (2.77)	3.27 (2.40)	3.06 (2.81)	2.21 (2.15)	0.80 (0.922)	27.4 (<0.00001)
IBS severity[ǂ]	2.00 (0.544)	2.07 (0.704)	2.00 (0.612)	1.95 (0.405)		
IBS duration (years)	11.1 (7.73)	16.5 (9.78)	9.06 (6.06)	8.47 (5.98)		

[ǂ]
on a scale of 0 (None: no symptoms), to 4 (Very severe: markedly affects my lifestyle)

[¥]
depression and anxiety were measured on the HADS; possible scores for each of anxiety and depresssion range from 0 to 21

IBS-C, IBS-D, and IBS-A, constipation, diarrhea, and alternating, respectively.

Table 2

Cluster corrected results from GLMs

The column labels indicate the factors used as covariates. IBS-C (n=15), IBS-D (n=17), IBS-A (n=19), pain predominant (n=17), and non-pain predominant (n=38) refer to GLMs in which these subgroups are compared to controls, with age as a covariate.

cluster	side	Peak x,y,z	T-val	age vol	age pval	age/anx vol	age/anx pval	age/dep vol	age/dep pval	age/anx/dep vol	age/anx/dep pval	IBS-C pval	IBS-D pval	IBS-A pval	pain pval	non-pain pval
control>IBS																
PPC	left	-38 -53 69	4.45	6550	0.00002	11046	0.00000	19935*	0.00000	4006	0.00037		0.02250	0.00018		0.03706
MFG	left	-47 46 18	4.32	5407	0.00007	8291	0.00000	14158*	0.00000	1368	0.01989	0.03333	0.02720		0.01029	0.00014
thalamus bilat	left	-12 -29 -4	3.66	4901		205	0.32757	1637	0.01218				0.06771			0.12237
	right	13 -29 -2	3.36		0.00012	1399	0.01876						0.00028	0.00189		0.00141
temporal	right	30 26 -36	3.72	3668	0.00057	5001	0.00011	7259	0.00001	3144	0.00116					0.24716
vstr bilat	left	-14 14 -13	3.94	3042	0.00134										0.00203	
	right	22 12 -12	3.47												0.00097	0.00081
mPFC	left	-7 55 9	4.56	2244	0.00442	2003	0.00653	14158*	0.00000			0.02640				0.00153
precun	right	8 -77 64	3.72	2227	0.00454	7479	0.00001	19935*	0.00000	3887	0.00043	0.02692				
temporal	left	-59 -30 -11	3.39	1905	0.00768					4707	0.00015			0.00605		0.00089
PM6	left	-38 0 37	4.02	1363	0.02008	1417	0.01814	1344	0.02081				0.01538			0.01825
vlPFC	right	27 67 -4	3.56	1303	0.02250			2651	0.00237						0.00354	
occipital	left	-21 -79 11	4.70	1095	0.03392	1272	0.02389	969	0.04409							0.04818
STG	right	46 -27 11	3.52	1001	0.04120	1671	0.01147	1924	0.00744							
Fr pole	left	-21 60 -15	3.73	982	0.04289			14158*	0.00000	4162	0.00030				0.00209	0.00153
putamen	*left*	-31 -11 11	2.95	888	0.05250					1396	0.01887					
vlPFC	*left*	-39 40 -9	3.68	768	0.06873			14158*	0.00000						0.04337	
vlPFC	right	55 38 26	3.09	703	0.08001	4921	0.00012									
IBS>control																
pACC	left	-3 30 9	3.14	1156	0.03000	1078	0.03512						0.01838			0.00027
OFC	left	-41 38 -22	3.53	983	0.04280										0.00064	
dLPFC	*left*	-42 19 34	3.91	745	0.07249											0.02648
Hc/pHc	*left*	-38 -59 -14	4.02	740	0.07334			923	0.04865	2390	0.00352	0.03333				0.00960
Hc/pHc	*right*	31 -42 -19	3.44	641	0.09291					926	0.04834					

cluster	side	Peak x,y,z			T-val	age vol	pval	age/anx vol	pval	age/dep vol	pval	age/anx/dep vol	pval	IBS-C pval	IBS-D pval	IBS-A pval	pain pval	non-pain pval
Hc/pHc	left	-30	-32	-22	3.40	639	0.09337					2390	0.00352					0.00960
S2/pINS	right	46	-26	23	3.27	621	0.09761											0.01308

Peak x,y,z, coordinates in MNI/ICBM standard for analysis with age as covariate; Tvalue refers to that peak. vol, volume in mm³; pval, corrected (cluster level) p-value; PPC, posterior parietal cortex; thalamus bilat, bilateral thalamus, midbrain; vStr bilat, bilateral ventral striatum; vlPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; precun, precuneus; PM6, premotor Brodmann area 6; sTG, superior temporal gyrus; pACC, pregenual ACC; OFC, orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex; Hc/pHc, hipposcampus/parahippocampal gyrus; S2/pINS, secondary somatosensory cortex, posterior insula.

*
indicates that cluster contains multiple regions.