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SYSTEMATIC REVIEWS

Neuroimaging the brain-gut axis in patients with irritable bowel syndrome

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Abstract

AIM: To summarize and synthesize current literature on neuroimaging the brain-gut axis in patients with irritable bowel syndrome (IBS).

METHODS: A database search for relevant literature was conducted using PubMed, Scopus and Embase in February 2015. Date filters were applied from the year 2009 and onward, and studies were limited to those written in the English language and those performed upon human subjects. The initial search yielded 797 articles, out of which 38 were pulled for full text review and 27 were included for study analysis. Investigations were reviewed to determine study design, methodology and results, and data points were placed in tabular format to facilitate analysis of study findings across disparate investigations.

RESULTS: Analysis of study data resulted in the abstraction of four key themes: Neurohormonal differences, anatomic measurements of brain structure and connectivity, differences in functional responsiveness of the brain during rectal distention, and confounding/correlating patient factors. Studies in this review noted alterations of glutamate in the left hippocampus (HIPP), commonalities across IBS subjects in terms of brain oscillation patterns, cortical thickness/gray matter volume differences, and neuroanatomical regions with

increased activation in patients with IBS: Anterior cingulate cortex, mid cingulate cortex, amygdala, anterior insula, posterior insula and prefrontal cortex. A striking finding among interventions was the substantial influence that patient variables (*e.g.*, sex, psychological and disease related factors) had upon the identification of neuroanatomical differences in structure and connectivity.

CONCLUSION: The field of neuroimaging can provide insight into underlying physiological differences that distinguish patients with IBS from a healthy population.

Key words: Irritable bowel syndrome; Neuroimaging; Brain-gut axis; Functional magnetic resonance imaging

Core tip: The present study reports replicable evidence that persons with irritable bowel syndrome have differences in brain structure and function when compared to healthy volunteers. Gender, psychological factors, and gastrointestinal symptom distress substantially influence these findings.

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most common condition encountered by gastroenterologists, and yet efficacious treatments have not been discovered that provide patients with satisfactory relief[1]. The diagnosis of IBS is based according to Rome Ⅲ criteria, which requires patients to experience recurrent abdominal pain or discomfort for at least three days per month in the last three months, in addition to their pain being associated with two or more of the following: Improvement in pain with defecation, pain onset associated with a change in the form of stool, or pain onset associated with a change in the frequency of stool[2]. Worldwide prevalence rates of IBS are approximately 11%, with the following countries reporting highest prevalence estimates of over 20%: United States, Taiwan, United Kingdom, Greece, Peru, Croatia, Iceland and Nigeria[3]. The prevalence of IBS is slightly higher in women than in men, and patients are typically categorized into a subgroup based upon their predominant bowel habit: Diarrhea-predominant, constipation-predominant, or a mixture of both[4]. Although IBS occurs in all age groups, the prevalence of IBS is lower in those persons over 50 years of age[5].

The disorder of IBS is associated with adverse physical, psychosocial and socioeconomic consequences for patients and society at large. IBS is not associated with increased rates of mortality but is associated with physical distress, often co-occurring with other debilitating conditions such as fibromyalgia, chronic pelvic pain and chronic fatigue syndrome[3]. Patients with IBS often suffer from psychological disorders such as depression and anxiety, with reported comorbidity rates of 40%-60% and above[6]. Numerous investigations have found IBS to exert a negative impact upon patients' quality of life, as well as result in the disproportionate utilization of health care resources[7]. In addition, financial estimates of managing the disorder are upwards of one billion dollars in the United States; a figure compounded by costs of lost productivity and reduced leisure time[8]. Although significant advances in understanding the pathophysiology of this disorder have been gained by research endeavors, exact mechanisms underlying symptom generation in IBS remain incompletely understood[9].

The "brain-gut axis" (BGA), is a collective term describing pathways between physiological systems noted to be altered in patients with IBS, and is composed of the enteric nervous system, autonomic nervous system and/or the central nervous system[10]. The BGA is a comprehensive framework within which symptom etiology can be evaluated in patients with IBS, as it accounts for the crosstalk or bidirectional communication that occurs between systems[11]. Alterations in the BGA of IBS patients have been shown to include peripheral factors, central and autonomic neural functions, hormones, amines and peptides[12]. Research efforts have also incorporated neuroimaging techniques to evaluate central mechanisms within the BGA, investigating neuroanatomical differences that may shed light on IBS symptomatology.

A Rome Working Team Report in 2009, focusing upon brain imaging and functional gastrointestinal disorders, summarized neuroimaging studies from 1997 onwards that evaluated IBS patients and healthy controls in response to visceral stimuli[13]. This review reported IBS patients experience greater activation of the insula (INS), anterior cingulate cortex (ACC), thalamus (THAL), and prefrontal cortex (PFC) in response to rectal distension. These findings are similar to the reproducible findings seen in response to pain stimuli across a variety of clinical disorders[14]. However, the majority of studies did not control for relevant factors such as affective comorbidity, patient sex, or anxiety related to symptoms that may have impacted these findings.

In an attempt to create a consensus regarding differential regions of brain activation between IBS patients and healthy controls, Tillisch *et al*[15] performed a meta-analysis of pooled neuroimaging data across eighteen rectal distension studies. These authors

reported that IBS patients and healthy controls activate similar brain regions involved in visceral afferent processing [*e.g.*, INS, anterior midcingulate cortex (aMCC), THAL], but noted IBS patients showed greater activation of the emotional arousal regions [*e.g.*, sgACC, amygdala (AMG)], as well as engagement of the midbrain. Although this investigation provided synthesis of neuroimaging data from disparate studies, the authors did not account for the influence of patient variables (*e.g.*, sex, bowel habit, psychological comorbidities) due to the nature of their analyses. The influence of patient variables, heterogeneity in the IBS patient population, variations in study methodology, and neuroimaging findings which overlap with other pain and psychological disorders, makes the discovery of IBS-specific neuroanatomical findings a complex endeavor.

The field of neuroimaging continues to rapidly advance, however, with new techniques to investigate the BGA in patients with IBS. Tillisch *et al*[16]'s article on advances in neuroimaging, provided an overview of 5 techniques that were pertinent to this review: Functional magnetic resonance imaging (fMRI), connectivity analysis, resting state fMRI (rs-fMRI), structural MRI (sMRI) and diffusion tensor imaging (DTI). First the authors reported that fMRI was able to measure moment-to-moment alterations in the oxygen content of blood (the blood oxygen level dependent or BOLD signal). Increases in BOLD activity correlated with increases in neuronal activity, making it possible to estimate the amount and anatomic location of brain activity that occurred during a particular stimulus, such as sorting cards, facial matching, or pain induction with rectal distention. Second, connectivity analysis utilized the same fMRI technique, however, focused on network patterns or circuitry between different brain regions. Third, rs-fMRI evaluated spontaneous brain activity of intrinsic brain networks that took place during a wakeful state. Fourth, sMRI evaluated cortical thickness as well as white and gray matter (GM) volume or density on a global, regional and local scale. Fifth, the authors reported DTI took advantage of the diffusivity of water that evaluated white matter (WM) anatomy and integrity as a function of fractional anisotropy (FA). Some of the networks investigated in neuroimaging studies included salience/executive control, cognitive control, cerebellar, left frontal parietal, right frontal parietal and default mode networks[17]. Lastly, it is important to mention magnetic resonance (MR) spectroscopy that measured relative concentrations of metabolite and neurotransmitter in areas of the brain[18].

Persistent symptomatology in the IBS patient population and ineffective current therapies, require ongoing efforts to understand the etiology and perpetuation of symptoms in patients with IBS. Neuroimaging is one investigative technique to assess central mechanisms in patients with IBS, and may shed light on BGA functioning and relate its relationship to symptom expression. Significant findings have been reported by prior investigations, but ongoing research efforts and technological advances warrant a reappraisal of progress made in the field. Therefore, a literature review was undertaken with the following goal in mind: To summarize and synthesize the literature on neuroimaging the BGA in patients with IBS.

MATERIALS AND METHODS

The following databases were searched in February of 2015 to explore articles on the topic of interest: PubMed, Scopus and Embase. Publication dates were filtered from the year 2009 and onward, as the Rome Working Team Report was published in 2009, and the field of neuroimaging is rapidly advancing. Studies were limited to those written in the English language and those conducted upon human subjects. The following terms were selected as keywords to conduct this review: "irritable bowel syndrome" or "IBS" AND "brain gut axis" or "BGA", "autonomic nervous system" or "ANS", "hypothalamic pituitary adrenal axis" or "HPA axis", "neuroimaging" or "brain scans" or "MRI". Each of the four pairs of terms (BGA, ANS, HPA and neuroimaging) were run separately with IBS as search terms in order to comprehensively cover the subject area of interest. Searches were then re-run without date constraints or filters, in order to capture articles published online ahead of print that otherwise would not be displayed.

The initial search yielded a total of 797 articles: PubMed (193), Scopus (302) and Embase (302). All titles and relevant abstracts were scanned for consideration of inclusion, with review articles being excluded as the interest was upon primary research investigations conducted in patients with IBS. Thirty-eight articles were pulled for full text review, with articles subsequently excluded if the investigation did not include a healthy control group against which to compare patients with IBS, if an article detailed data from an investigation previously accepted for review, and if the article (n = 1) was previously included in the meta-analysis by Tillisch *et al*[15]. Twenty-seven articles fulfilled the inclusion criteria and were reviewed to determine study design, methodology and results. The following data points were then placed in table format to elicit analysis and synthesis of data across studies: 1st Author, Year, Country, Sample Size, Participant Stratification, Imaging Modality, Study Details, Interventions, Major Findings Across Studies, Individual Findings, Physiological Correlations, Significant Inventory Differences, Confounding and Correlating Factors. Major findings that focused on anatomical areas were then tabulated across studies to determine the most prevalent findings. Assessment of study findings included not only isolated areas of brain activation or deactivation, but also differences in patterns of connectivity across brain regions between patients with

IBS and healthy controls. Lastly, individual study findings that included the identification of confounding or correlating patient factors were examined for commonalities in efforts to integrate findings from disparate investigations.

RESULTS

Analysis of study data resulted in the abstraction of four key themes: Neurohormonal differences, anatomic measurements of brain structure and connectivity, differences in the functional responsiveness of the brain during rectal distention, and confounding/correlating patient factors (Table 1). The first three themes identify differences between patients with IBS and healthy controls, whereas the fourth illuminates factors that influence the identification of such differences or interpretation of findings. Patient inventories that differed significantly between patients with IBS and healthy controls are displayed in tabular format. All 27 studies utilized neuroimaging techniques to assess the BGA in patients with IBS, and are grouped according to imaging modality to facilitate comparisons across disparate investigations.

Magnetic resonance spectroscopy

Niddam *et al*[19] utilized proton magnetic resonance spectroscopy (H-MRS) in an investigation of HPA axis dysregulation in patients with IBS. To gain insight of the stress response system, metabolite concentrations of excitatory Glutamate (Glu) and Glutamine (Gln) were measured to assess the HIPP inhibitory feedback to the HPA axis. Reduced concentration of metabolites Glu-Gln (Glx) were reported in the left HIPP of IBS patients (n = 15) *vs* healthy controls (n = 15), P = 0.04. Further, Glx metabolite concentrations in IBS patients were negatively correlated with state anxiety (r = -0.741) and catastrophizing (r = -0.633).

sMRI

In an investigation that explored the contribution of patient variables to altered brain structure, Blankstein *et al*[20] compared patients with IBS (n = 11) to healthy controls (n = 16) using sMRI with voxel-based morphometry (VBM) and cortical thickness (CT) analysis. IBS patients were found to have increased HYP GM and decreased cortical thickness in the aMCC in comparison to controls. When age was accounted for, a negative correlation was found between the thickness of the dorsolateral prefrontal cortex (dlPFC) and scores on the pain catastrophizing scale (PCS) (r = -0.66), in contrary a positive correlation was found between the thickness of the aINS and the duration of patient pain (r = 0.78).

In a larger sample, Seminowicz *et al*[21] utilized sMRI with VBM and CT analysis to investigate anatomical brain differences in female patients with IBS. Initially these researchers found numerous differences in GM density between IBS patients (n = 56) and healthy controls (n = 49). However, after adjusting for anxiety and depression, GM density decreased in the left posterior parietal cortex, left MFG, and bilateral temporal cortices in IBS patients. These differences in GM density were largely consistent across subgroups that categorized patients based on predominant bowel habit as well as pain *vs* no-pain as most bothersome IBS symptom. They also reported a small negative correlation (r = -0.35) between IBS duration and GMD in the dorsolateral PFC, but only in the non-pain predominant group.

In a study that compared healthy subjects to those with inflammatory *vs* non-inflammatory types of visceral abdominal pain, Hong *et al*[22] utilized sMRI to examine IBS subjects with diarrhea (n = 11), subjects with ulcerative colitis (UC) (n = 16) and healthy controls (n = 41). In comparison to healthy controls, IBS subjects were found to have significantly lower grey matter CT in the right aINS; a difference that remained significant when anxiety and depression were controlled for in statistical analyses. This regional difference was distinct from those reported between subjects with UC and healthy controls, and significant correlations were not found between CT and patient variables in the IBS group.

Jiang *et al*[23] evaluated regional GM changes as a function of sex in patients with IBS using sMRI. Comparing patients with IBS (n = 90) to healthy controls (n = 176), initially no differences in whole brain CT were found. However, when separating groups by sex and disease, female patients with IBS were found to have diminished CT in bilateral sgACC, as well as greater CT in pre and post central gyrus (PoCG) in comparison to female healthy controls. Region of interest (ROI) analysis revealed female IBS patients have significantly smaller CT in bilateral aINS, medial INS, pINS and left sgACC compared to female healthy controls. Differences in CT were found in female IBS patients in the right pINS that were dependent on their bowel subtype (diarrhea *vs* constipation), as well as by sex (males having greater CT in right sgACC). Correlations of patient variables with CT revealed female IBS patients to have negative correlations between length of disease and CT in right mINS (r = -0.293), as well as anxiety symptoms with CT in right aINS (r = -0.273) and right mINS (r = -0.248). Correlations of patient variables with CT in male IBS patients included symptom severity with CT in left mINS (r = -0.673), trait anxiety with CT in sgACC (r = - 0.525) and in right pINS (r = 0.469), as well as early trauma inventory (ETI) with CT in left mINS (r = 0.556).

The relevance of patient variables was also reported by Labus *et al*[24] in an investigation of pooled sMRI studies examining GM volume and regional brain network alterations in female patients with IBS. Initially numerous differences were identified between IBS patients (n = 82) and healthy controls (n = 119) when

Table 1 Neuroimaging the brain-gut axis in patients with irritable bowel syndrome

Ref.	Year	Country	Imaging	NI	F	M	CN	ACC	MCC	AMG	HIP	HYP	aINS	pINS	PFC	PoCG	THAL	Inven Diff	Conf/corr
Niddam *et al*[19]	2011	Taiwan	MRS	15	8	7	15				-							-	A (st), PCS
Blankstein *et al*[20]	2010	Canada	sMRI	11	11	0	16		-			+						-	Dz, PCS
Seminowicz *et al*[21]	2010	United States	sMRI	56	56	0	49											A, D	A, D, Dz
Hong *et al*[22]	2014	United States	sMRI	11	9	2	41						-R					A, C, D, S, V	-
Jiang *et al*[23]	2014	United States	sMRI	90	70	20	176	- B					-B	-B		+L		A, C, D, E, S	A, Dz, ETI, Sb, Sx
Labus *et al*[24]	2014	United States	sMRI	82	82	0	119			-R						+L		A, C, D, E	Dz, ETI
Piché *et al*[25]	2013	Canada	sMRI	14	14	0	14							+R				A, C, D	Dz
Berman *et al*[26]	2012	United States	sMRI/PET	11	5	6	11	+B		+R				+R				N, VSI	ETISF
Chen *et al*[27]	2011	Canada	MRI-DTI	10	10	0	16							+R				-	Dz, N, PCS
Ellingston *et al*[28]	2013	United States	MRI-DTI	33	21	12	93	+B									-B	-	Dz, Sx
Ma *et al*[29]	2014	China	rs-fMRI	21	7	14	21				-R					-B		NA	Dz
Hong *et al*[30]	2013	United States	rs-fMRI	60	31	29	118			+L	+R		+B					A, D, N, V	Dz, Sx
Hong *et al*[31]	2014	United States	rs-fMRI	48	24	24	48						-L					A, D, V	Dz, VSI
Gupta *et al*[17]	2014	United States	rs-fMRI	58	28	30	110	+B	+R				+B[1]	+R			+L	A, D, E, N	ETI, Sx
Aizawa *et al*[41]	2012	Japan	fMRI	30	15	15	30				-R			+L	-R			-	-
Labus *et al*[42]	2013	United States	fMRI	47	27	20	67			+R								A, D	A, D, Sx
Hubbard *et al*[43]	2011	United States	fMRI	14	14	0	17		+L	+L		+L						A (tr)	A (st & tr)
Kilpatrick *et al*[44]	2011	United States	fMRI	26	26	0	29			+L	+L							-	Genotype
Hall *et al*[32]	2009	Canada	fMRI-RD	7	7	0	6	+R					+L[1]		+B			NA	-
Larsson *et al*[33]	2012	Sweden	fMRI-RD	44	44	0	20	+L			+R		+R	+L	+L		+L	A, D	Subgrps of Pain
Elsenbruch *et al*[34]	2010	Germany	fMRI-RD	15	15	0	12		+L				+L[1]		+L			A	A
Icenhour *et al*[35]	2015	Germany	fMRI-RD	17	15	2	21	+R	+L	+L					+		+	A, C, D, N	A
Bouhassira *et al*[36]	2013	France	fMRI-RD	20	20	0	11											HAD -t	HAD, PCS
Lee *et al*[37]	2012	Taiwan	fMRI-RD	17	11	6	17		+B				+L[1]		+B			A, HAD -t	A
Schmid *et al*[38]	2015	Germany	fMRI-RD	17	15	2	17		+B		+L							A, D, N	D
Lowén *et al*[39]	2013	Sweden	fMRI-RD	44	44	0	18	+B	+L		-L		+R	+R	+L			-	-
Labus *et al*[40]	2011	Netherlands	fMRI- RD	14	14	0	12			+					+			A, D	-

[1]Results reported for insula *vs* aINS; +: Activation/increased connectivity; -: Deactivation/decreased connectivity; A: Anxiety; A (st): State anxiety; A (tr): Trait anxiety; ACC: Anterior cingulate cortex; AMG: Amygdala; aINS: Anterior insular cortex; B: Bilateral; C: Catastrophizing; CN: Control group sample size; Conf/Corr: Confounding/correlating variables; D: Depression; Dz: Disease variables; E or ETI: Early trauma inventory; ETISF: Early trauma inventory short form; F: Female; fMRI: Functional magnetic resonance imaging; HAD: Hospital Anxiety and Depression Index; HAD-t: Hospital Anxiety and Depression Index Total Score; HIP: Hippocampus, HYP: Hypothalamus; Inven Diff: Inventory differences; L: Left; M: Male; MCC: Mid cingulate cortex; MRI-DTI: Magnetic resonance imaging - diffusion tensor imaging; MRS: Magnetic resonance spectroscopy; NI: Sample size of IBS patients; N: Neuroticism measured *via* NEO-PI (five factor inventory for personality); NA: Not assessed; PCS: Pain Catastrophizing Scale; PET: Positron emission tomography; PFC: Prefrontal cortex; pINS: Posterior insular cortex; PoCG: Post central gyrus; R: Right; RD: Rectal distension; S: Somatization - PHQ score (Patient Health Questionnaire); rs-fMRI: Resting state functional magnetic resonance imaging; Sb: Bowel subgroup; Sx: Patient sex; sMRI: Structural magnetic resonance imaging; THAL: Thalamus; VSI: Visceral sensitivity index.

aggregating data across seven neuroimaging studies. However, once the authors accounted for early life events *via* the ETI, the majority of group differences between IBS patients and controls were no longer statistically significant. Only the findings of reduced GM in the right AMG and higher GM in the left PoCG remained to differentiate patients with IBS from healthy controls. In addition, small correlations were reported between IBS symptoms and GM volume changes, that included associations between left INS and symptom severity (r = -0.26), as well as right inferior frontal gyri and disease duration (r = -0.26).

Piché *et al*[25] conducted an investigation that explored brain morphology, pain inhibition, and associations with disease in female patients with diarrhea-predominant

IBS. The study compared IBS patients (n = 14) to healthy controls (n = 14), and used sMRI to evaluate the reaction to electrical stimulation and heterotopic noxious counter-stimulation (HNCS). IBS patients did not differ from controls in terms of shock pain ratings nor cold pain stimulus (HNCS), but did differ in terms of decreased pain inhibition (P = 0.02). In addition, IBS patients were found to have a thicker right pINS; a finding that remained significant when patient variables were controlled, and was positively correlated with duration of IBS (r = 0.67), but not the severity of IBS.

Berman *et al*[26] used noradrenergic (NE) receptor antagonists, agonists, and placebo, and assessed differences between IBS patients (n = 11) and healthy controls (n = 11) in central NE signaling during an auditory vigilance task. IBS patients were found to have higher baseline levels of plasma NE, and through positron emission tomography and sMRI, were shown to experience less reduction of activity in a central arousal circuit (bilateral sgACC, left pregenual ACC, right AMG, left dorsal brainstem and right pINS) by Yohimbine (YOH), a NE antagonist, in comparison to healthy controls. Although IBS patients and healthy controls were not found to differ in pre-ingestion levels of anxiety, YOH increased anxiety more in IBS patients (P = 0.011), and the increased anxiety correlated with plasma NE levels in IBS patients (r = 0.61) but not in healthy controls. Clonidine (CLO), a NE agonist, was found to increase left sgACC activity more in patients with IBS than in healthy controls. Lastly, the inhibitory effect of YOH was found to inversely correlate with early life trauma in the left dorsal brain stem and left AMG, although group differences could not be assessed due to missing data.

Across investigations employing sMRI, the two most consistent anatomical findings were reduced CT in the aINS and increased CT/GM volume in the PoCG in female patients with IBS. Anatomic alterations commonly correlated with patient variables such as sex, anxiety, depression, IBS bowel subtype and early life trauma. Negative correlations were found between dlPFC with PCS scores and with IBS symptom duration, and between the INS with anxiety and with IBS symptom severity.

DTI

Chen *et al*[27] used MRI DTI and investigated WM abnormalities in female patients with IBS. FA was used as a measure of microstructural WM integrity. The researchers evaluated pre-selected areas associated with nociception, and reported that patients with IBS (n = 10) had an increased FA in the fornix and in the external capsule bordering the right pINS in comparison to healthy controls (n = 16). Additionally, the relationship between FA and patients' disease and personality characteristics was explored with the following correlations reported: Pain severity and FA in bilateral aINS (r = 0.71) and right ventral posterior lateral nucleus of the THAL (r = 0.576), unpleasantness and FA in left aINS (r = 0.790), duration and FA in left pINS (r = 0.662), neuroticism and FA in left medial dorsal nucleus of the THAL (r = 0.685), as well as PCS scores and FA in right mACC (r = -0.764).

Ellingson *et al*[28] also utilized DTI in an investigation of alterations in brain microstructure in patients with IBS (n = 33) in comparison to healthy control subjects (n = 93). These researchers found IBS patients to have diminished FA (low directional coherence) in bilateral THAL, bilateral globus pallidus, bilateral putamen, bilateral primary and secondary somatosensory and motor regions, as well as in bilateral PCC, and found increased FA (high directional coherence) in bilateral frontal lobe, bilateral ACC and corpus callosum. Similar to study findings previously reviewed, these investigators found differences in surrogate measures of brain microstructure dependent upon IBS and patient sex. Although such differences were not found among healthy controls, female IBS patients were found to have lower FA in the THAL and primary sensory and motor regions in comparison to male patients with IBS. Correlations between symptom severity and DTI were also examined: No significant correlations were found for female patients with respect to FA, although male patients were found to have negative correlations between symptom severity and average FA in the ACC (R^2 = 0.4199), BG (R^2 = 0.4793) and WM regions near the INS (R^2 = 0.4086).

Across the two investigations employing DTI, consistent areas of FA were not reported. In terms of patient variables, sex was noted by the second investigation to influence study findings. Lastly, although correlations were noted for female patients in the first investigation between FA with patient variables, significant correlations for female patients were not reported by the second.

rs-fMRI

rs-fMRI was employed by Ma *et al*[29] in an investigation of brain alterations in patients with IBS. Through investigation of the differences between IBS patients (n = 21) and healthy controls (n = 21) in amplitude of low-frequency fluctuation (ALFF) and ROI based functional connectivity, IBS patients were reported to have diminished amplitude in the left SFG, right HIPP, right MFG, bilateral PoCG and right superior temporal pole, as well as increased ALFF in the left calcarine and left MCG. Correlations were found between disease duration and ALFF values in the left MCG (r = -0.477) as well as in the right MFG (r = 0.517). Lastly, in comparison to healthy controls, IBS patients were found to have increased connectivity between the left MCG and left SFG, revealing increased connectivity between the cingulate and frontal cortex.

Hong *et al*[30] utilized rs-fMRI to investigate the dynamics of resting brain activity in patients with chronic visceral pain. Additionally, the effect of sex on

brain activity in patients with IBS (n = 60) and healthy controls (n = 118) was assessed. Similar to findings of previously reviewed investigations, no differences were initially found when males and females were grouped together; however, significant differences between groups were noted once separated by sex. The study also evaluated differences in resting-state brain function (spontaneous brain frequency oscillations) with fractional amplitude of low-frequency fluctuation (fALFF) at three different frequencies: Low (LF), medium (MF) and high (HF). Female IBS patients were found to have increased frequency power distribution in the left AMG, right HIPP and bilateral aINS, and LF power distribution in the sensorimotor regions when compared with female healthy controls and with male patients with IBS. In addition, a correlation between abdominal discomfort and HF power distribution in the left aINS (r = 0.506) was found for female subjects with IBS.

Building upon these findings, Hong *et al*[31] performed an rs-fMRI investigation of patients with IBS (n = 48) in comparison to healthy controls (n = 48), exploring the effect of sex and disease upon brain connectivity patterns of the dorsal aINS. Connectivity differences were reported between the sexes, as were reports of differences as a function of sex and disease. For instance, in comparison to female healthy controls and male patients with IBS, female IBS patients were found to exhibit a greater negative connectivity between bilateral dorsal aINS to bilateral PFC regions, as well as between the left dorsal aINS to the left precuneus. Correlations were reported for male IBS patients, between connectivity of the bilateral dorsal aINS with the bilateral dorsal medial PFC and the Visceral Sensitivity Index, (left r = 0.442, right r = 0.405), and between the left dorsal aINS and left mPFC (r = 0.41). Correlations were also reported for female IBS patients, between connectivity of the left dorsal aINS to the precuneus with symptom intensity (r = 0.597), and between the bilateral dorsal aINS to the bilateral dorsal mPFC (left r = 0.497, right r = 0.466).

The influence of patient variables was also evaluated by Gupta *et al*[17] in a pooled rs-fMRI investigation of early adverse life events (EAL) and sex in patients with IBS and healthy controls. Comparing 58 IBS patients with 110 healthy controls, increased BOLD oscillation intrinsic connectivity patterns in the left frontal parietal, salience, and default mode networks [regions including, but limited to bilateral INS, bilateral ACC, right MCC, left THAL, right supramarginal gyrus (SMG) and right precuneus] were found. The effect of EAL was examined and the authors reported reduced connectivity in the salience/executive control network in female and male patients with IBS compared to healthy controls: Bilateral INS, bilateral ACC, left supplementary motor area (SMA) and left parietal and frontal regions, as well as increased connectivity in the left putamen. Lastly, male patients with IBS and EALs were found to have alterations of increased connectivity in the cerebellar network: Left THAL, right pINS, bilateral ACC, right cerebellum and left middle temporal gyrus. These patterns of connectivity were greater than in male healthy controls with EALs, and were not found in female participants (IBS or healthy controls).

Across rs-fMRI investigations, congruence was found with increased oscillation patterns in the INS, although conflicting findings were reported for the right HIPP. Patient variables of sex and early life trauma were found to influence study findings. In addition, correlations were reported between patient variables and neuroimaging findings, primarily relating to disease characteristics and psychological factors.

fMRI using rectal distension paradigms

Since 2009, there have been additional fMRI studies that utilized rectal distension protocols to investigate differences between IBS patients and healthy controls, 9 of which met the inclusion criteria for this review. Hall *et al*[32] utilized a single rectal distension protocol and fMRI to evaluate female patients with IBS (n = 7) in comparison to healthy controls (n = 6). IBS patients were found to experience heightened activation during painful rectal distension in the right ACC, left INS and ventral medial prefrontal regions, as well as a failure to down-regulate activation of bilateral vmPFC during the tonic phase (constant state) of the distension protocol.

Larsson *et al*[33] investigated differences between female subjects with IBS (n = 44) and healthy controls (n = 20), using fMRI and a high/low rectal distension paradigm. IBS subjects were found to experience greater activation in the left vlPFC during high distension, greater activation in left mINS during low distension, and greater activation in right aINS, right mINS and right HIPP during expectation of high distension. Further differences were noted within IBS patients when stratifying according to subtype of pain (normosensitive *vs* hypersensitive), although the two groups did not differ in scores of anxiety, depression, disease duration or severity. For example, normosensitive patients did not differ significantly from healthy controls in brain responses during active distension, but did experience greater activation in the right HIPP during expectation of high stimulus distension. Hypersensitive patients, in contrast, were found to differ significantly from healthy controls in brain responses during high rectal distension, showing increased activation in the left pINS, left THAL and left pACC.

Elsenbruch *et al*[34] investigated the role of emotional context on visceral stimuli response in patients with IBS, utilizing fMRI, painful/non-painful rectal distensions and environmental manipulation (progressive muscle relaxation and a public speaking stressor). Analysis of group responses to stress revealed female IBS patients (n = 15) with increased activation in the left aMCC and left vlPFC during nonpainful distension, and with greater activation in the right INS and left vlPFC during painful distensions in comparison to healthy controls (n = 12).

These findings remained significant after including anxiety as a covariate, and anxiety was noted to explain diminished relaxation response.

Alterations in fear learning and extinction in IBS patients was evaluated by Icenhour *et al*[35], using a rectal distension protocol to promote learning, extinction and reinstatement. Study analysis of IBS patients (n = 17) and healthy controls (n = 21) also included fMRI, skin conductance responses as well as salivary analysis for cortisol and alpha-amylase. The authors report group differences to be greatly affected by the inclusion of anxiety as a covariate, and yet significant findings remained. In comparison to healthy controls, IBS patients exhibited increased activation of the right ACC, left MCC and left AMG during fear learning, the THAL during extinction, and the dmPFC, right ACC and left MCC during reinstatement. The influence of sex upon findings was also investigated in an exploratory analysis between females with IBS (n = 15) and healthy controls (n = 10), with the authors confirming differences noted between groups in the full sample.

Bouhassira *et al*[36] investigated pain processes in female patients with IBS, constipation predominant (n = 20), in comparison to healthy controls (n = 11), using slow-ramp rectal distension. These investigators used fMRI, assessed diffuse noxious inhibitory control of pain, and categorized IBS patients into two groups based upon the following: Inhibition (I) or facilitation (F) of RIII nociceptive spinal reflex (measured on the left lower limb). The two IBS groups did not differ in terms of clinical characteristics, although the Group F patients reported significantly higher IBS severity scores. When pooled together as a group a positive correlation was found between rectal sensation and two psychological inventories: HAD (r = 0.61) and PCS (r = 0.42). In addition, when pooled together as a group to analyze fMRI data, patients with IBS did not differ from healthy controls in areas of brain activation during non-painful distension, but did exhibit increased activation of various regions during painful rectal distension including the ACC, MCC, aINS, pINS, and THAL. However, once scores on the HAD or PCS were included as covariates, fMRI differences between groups were no longer significant.

Lee *et al*[37] investigated the effect of psychological factors upon patterns of brain activation during placebo analgesia, in a rectal distension protocol that compared IBS patients (n = 17) with healthy controls (n = 17). fMRI was used to analyze patterns of activity during anticipation and rectal distension while research subjects received inert substances along with suggestions of pain relief. Investigators reported comparable placebo effects among patients with IBS and healthy controls, however areas of brain activation during placebo analgesia differed between groups. For instance, upon rectal distension during placebo analgesia, IBS patients showed greater activation of the left INS, bilateral MCC, bilateral vlPFC and right precuneus in comparison to healthy controls. In addition, IBS patients had greater activation of the left vlPFC during anticipation of placebo. Lastly, in IBS patients, the HAD score for anxiety was negatively correlated with activation of the left vlPFC/INS (z-score = 3.69) during placebo analgesia, and was predictive of a weaker placebo effect.

Schmid *et al*[38] similarly investigated placebo analgesia in the context of visceral pain, and also found that patient variables influenced the placebo response. A rectal distension protocol was used in patients with IBS (n = 17), UC (n = 15) and healthy controls (n = 17), and fMRI assessed areas of brain activation during placebo analgesia. A negative correlation was found between patient variables and placebo analgesia response; however in this study, depression emerged as the relevant variable (r = -0.30). Unlike the prior investigation, however, IBS patients had dysregulated placebo response during rectal pain in comparison to healthy controls. Including depression scores as a covariate, IBS patients were found to have reduced down-regulation (or increased activation) in bilateral MCC, left HIPP, right PCC and right somatosensory cortex during rectal distension while undergoing placebo analgesia. Patients with UC did not experience this same dysregulated down-modulation. This study also assessed salivary cortisol levels as a marker of HPA axis dysfunction, but was unable to standardize collection times and did not find significant differences between groups.

Lowén *et al*[39] evaluated the neuroanatomical mechanisms of gut-directed hypnotherapy, in a rectal distension fMRI investigation of female IBS patients (n = 25) compared to healthy controls (n = 18). Prior to therapy initiation (either hypnotherapy or education intervention), patients with IBS who responded to treatment were found to have increased activation of the following regions in response to rectal distension: Left vlPFC, left aMCC, bilateral pACC and bilateral sgACC, as well as reduced activation of the left HIPP. During expectation of rectal distension, IBS patients, in comparison to healthy control subjects, had greater activation of the right ventral aINS and right dorsal pINS.

Alterations in the serotonin signaling system was investigated by Labus *et al*[40], comparing IBS constipation-predominant female patients (n = 14) to healthy control subjects (n = 12), who were administered an amino acid mixture to induce acute dietary tryptophan depletion (ATD). According to the authors, ATD has been shown as a reliable method to induce lower central and peripheral serotonin [5-hydroxytryptamine (5-HT)] levels. With the use of fMRI during a rectal distension protocol, healthy control subjects who underwent ATD were found to exhibit similar patterns of brain connectivity in an emotional arousal circuit as patients with IBS. Although subjects were studied under different

conditions, both groups during rectal distension were found to experience similarities of increased connectivity from the orbital medial prefrontal cortex (omPFC) to the AMG, and from the AMG to infragenual ACC.

Across fMRI investigations using rectal distension protocols, the following brain regions were consistently activated: ACC, MCC, AMG, aINS, pINS and PFC (primarily vlPFC). Patient variables that influenced study findings include anxiety, catastrophizing, and bowel subtype. In addition, patient psychological variables of depression and anxiety were reported to moderate the placebo response.

fMRI using other testing paradigms

Aizawa *et al*[41] utilized the Wisconsin Card Sorting Test (WCST) and fMRI, to explore associations between cognitive flexibility and neuroanatomical alterations in patients with IBS. No differences were found in WCST overall performance based upon IBS group or patient sex. In terms of fMRI results, patients with IBS were found to have decreased activity of right dlPFC, right HIPP and increased activity of left pINS at error feedback during set-shifting, as well as less connectivity from the dlPFC to the pre SMA in comparison to healthy controls. Duration of IBS symptomatology was not found to significantly correlate with either neuroimaging or WSCT results.

The influence of sex and disease was evaluated by Labus *et al*[42] using fMRI and a negative emotion face viewing paradigm to investigate emotion-related cognitive processes in patients with IBS. Neuroanatomical differences were not found between IBS patients (n = 47) and healthy controls (n = 67) until separating groups by sex. Male subjects with IBS were then found to experience greater activation in the right AMG compared to male healthy controls, whereas differences were not detected between females. IBS patients as a group showed lesser engagement of the HIPP to AMG circuit, although they exhibited stronger positive connectivity from the AMG to HIPP (with female IBS patients demonstrating the greatest connection). When accounting for patient variables of depression and anxiety, differences between male and female IBS patients revealed augmented activity for males in the HYP and aINS.

Hubbard *et al*[43] used a corticotropin-releasing factor antagonist, painful stimulus (transcutaneous abdominal electrical stimulation), and fMRI to look for evidence of HPA axis dysfunction in female patients with IBS. Baseline levels of ACTH were reduced in IBS patients (n = 14) *vs* healthy controls (n = 17), and although peripheral effects of HPA axis activity were not found after drug administration, fMRI data suggested evidence of central effects. In comparison to healthy controls, IBS patients were found to experience increased activation after placebo administration in the left HYP and left LCC during expectation of pain, as well as greater activity reduction in the left HYP after antagonist administration (both at low and high doses of drug). After inclusion of trait anxiety as a covariate into the analyses, differences in the left HYP remained significant only at the low dose of the drug. State anxiety was also found to moderate drug induced BOLD signal changes in the left HYP for average to high levels of anxiety. IBS patients were also found to exhibit a strong positive connectivity in an emotional-arousal circuit (*e.g.*, from aMCC to AMG and from AMG to HIPP). Antagonist administration significantly altered such connectivity, in that some IBS patients' path coefficients (*e.g.*, from HYP to AMG) resembled that of healthy controls' after placebo administration.

Alterations in the 5-HT signaling pathway in patients with IBS was investigated by Kilpatrick *et al*[44], in a study of serotonin gene polymorphism (HTR3A, c.-42C > T) assessed through salivary samples. These investigators used fMRI to evaluate AMG responsiveness during an affective matching paradigm in both female patients with IBS (n = 26) and healthy controls (n = 29). During a neutral visual task, IBS subjects were found to have greater activity in the left AMG and left HIPP in comparison to healthy controls, as well as increased left HIPP activity during the emotional task. In both IBS patients and healthy controls that carried the homogenous genotype, an association was found with increased anxiety and increased AMG responsiveness to neutral and emotional stimuli. Lastly, in patients with IBS who carried the homogenous genotype, an association was found with higher IBS symptom ratings, as well as a subset of patients who experienced low differential AMG activation, or difficulty discriminating between stimuli due to heightened engagement.

These fMRI studies did not reveal consistent neuroimaging differences between IBS patients and healthy controls. Likely this was due to variations in investigative focus and disparate study design. However, the influence of patient variables upon neuroimaging findings was noted across studies, and included patient sex, depression, anxiety as well as genotype.

DISCUSSION

The findings of this review reveal new developments in neuroimaging the BGA in patients with IBS. The field has continued to provide insight into underlying physiological differences that distinguish patients with IBS from a healthy population. These differences are wide-ranging, including differences in neurotransmitter concentrations, in gross and functional anatomic structure, and in functional brain responsiveness to rectal-distention. These cross-sectional observations and their correlation with sex, psychological factors, and gastrointestinal symptoms are an important scientific step towards understanding the pathophysiology of IBS.

As noted in prior reviews, there is a consistency in anatomical brain regions that are structurally and functionally different in patients with IBS than in healthy

volunteers. The greatest amount of consistency was seen with fMRI rectal distension studies, with increased BOLD activation of the ACC, MCC, AMG, aINS, pINS and PFC in IBS patients. This pattern of brain regions appear to represent a rectal-distention pain-related network and are similar to other pain-related networks[45]. These regions have been implicated in autonomic and neuroendocrine functioning, memory, interoception, consciousness, cognition and emotional arousal, among others[46]. The observations of heightened sensitivity of activation of the rectal-distension pain-related network in IBS also parallels the observations seen in other pain disorders[47,48]. The rectal distension paradigm demonstrates that IBS symptoms have a biologic foundation, but not one that is specific only to the IBS patient population.

Studies of anatomic structure are less consistent than seen with the rectal distention paradigm. While the two most consistent anatomical findings were reduced CT in aINS and increased CT/GM volume in PoCG in female patients with IBS, there is variability of structural results between the different studies. To date, only a small number of IBS studies focused on determining differences in the neurochemical constituents and functional connectivity patterns have been performed.

One striking finding was the influence of patient sex, psychological status, and disease related variables upon the identification of neuroanatomical differences between patients with IBS and healthy controls. These factors influenced results across the full spectrum of imaging modalities reviewed. Many of the studies reported results that were either sex-specific or sex-disease subtype specific. Sex hormones are increasingly recognized as influencing the BGA and contributing to the development of IBS symptomatology[49]. Many investigators in this review accounted for hormonal fluctuations in terms of scanner timing. However, the substantial differences in neuroimaging results suggest that IBS pathophysiology may not be uniform across gender.

Psychological factors, in particular anxiety, depression, early life trauma and catastrophizing, had substantial influence on the neuroimaging correlates of IBS. Of the 27 studies included in this review, 25 used validated inventories to assess the psychological characteristics of their study population, with 18 finding group differences in IBS patients. This stratification was of tremendous importance. Psychological variables confound the identification of IBS -specific neuroimaging group differences, as many of the imaging findings either positively or negatively correlated with psychological symptoms and tendencies. The majority of the reviewed studies reported associations between psychological inventories and neuroimaging findings, more so in fact than associations between disease characteristics and neuroimaging findings. The strength of such correlations varied between investigations, and although does not aid in determining causality of patient symptomatology, does reiterate the relevance of psychological factors in patients with IBS.

Many of the investigations also stratified subjects based upon their bowel subtype. The finding of decreased grey matter density of various areas of the brain was associated with IBS subtypes based on predominant bowel habit and predominance of pain symptoms. One innovation in IBS neuroimaging is the inclusion of UC patients as a comparison group for patients with IBS. Including a group that suffers from an organic disorder manifested by similar gastrointestinal symptomatology may help parcel out the various influences that contribute to IBS.

The ability to interpret the neuroimaging correlates of IBS and generalize them to the population is hindered by a number of limitations of the studies themselves. The studies were performed in nine different countries: United States (12), Canada (4), Germany (3), Sweden (2), Taiwan (2), China (1), Japan (1), France (1) and The Netherlands (1). Although this heterogeneity increases the generalizability of the results, and is relevant given the international prevalence of IBS, consideration must be given to the cultural context in which these studies are conducted. Cultural norms, at the very least, influence the acceptability of expressing symptomatology, the willingness to seek assistance for medical or psychological disorders, faith or distrust of the healthcare system, and the likelihood of participation in medical research. This leads to another issue that deserves mention: The self-selection of subjects who willingly agreed to participate in the aforementioned investigations. The study results are therefore reflective of this patient population, who may or may not represent the general IBS population at large. In addition, the sample size of the studies was noted to vary greatly, ranging from 13 to 266 participants. Therefore, the findings of these investigations need to be viewed in terms of their subject numbers and subsequent study power. All of the studies included in this review, except for two[34,35], matched IBS participants with a healthy control population of similar sex and age. The interpretation of the results of these two studies may be impacted by unmeasured age-related brain changes. Further aspects of sampling that need to be addressed include the stratification of participants by sex, IBS subtype, pain-type, and psychological characteristics. Nearly half of the studies in this review recruited female participants exclusively (n = 13). While using a homogeneous gender cohort typically decreases research variability, the gender-specific differences highlighted above suggest that such results cannot be generalized.

A final point for discussion is the inconsistencies that continue to permeate the results of neuroimaging studies, even when the best efforts are made to analyze a homogenous IBS patient population. As previously

mentioned, many neuroanatomical findings consistently replicated in the IBS patient population, are not specific to the IBS patient population. The heterogeneity of the patient population and the overlapping influence of psychological and physical pain disorders have made the identification of clinically relevant neuroanatomical findings a challenge. As neuroimaging results may display central changes between patients with IBS and healthy controls, we have yet to develop a consensus of the downstream effects of this structural snap shot or connectivity pattern as it relates to BGA functioning. The aforementioned studies provide evidence of the utility of neuroimaging in a disorder with innumerable intricacies.

The limitations of this review must be addressed in like fashion as the studies it has reviewed. First, only accepted literature for publication was included in this analysis, therefore results are subject to publication bias. Second, this review aimed to cover investigations that evaluated neuroimaging the BGA in patients with IBS. Additional neuroimaging pain literature may prove pertinent to this topic, but was outside the scope of this review. One final limitation is that this review is subject to the bias of the persons conducting it, from selection of articles, assessment and interpretation of findings as well as presentation of results.

IBS is a multi-factorial disorder, ridden with complexities, which exacts an exorbitant toll upon society' s financial and human resources. The manifestation of IBS symptomatology may occur anywhere along the BGA continuum, and has proven resistant, thus far, to curative medical treatment. Although great gains have been made by research endeavors in BGA dysfunction in patients with IBS, the development of symptomatology has remained elusive to our understanding.

The field of neuroimaging has provided insight into the underlying physiological differences that distinguish patients with IBS from a healthy population. Differences in neurotransmitter concentrations, differences in gross and functional anatomic structure, and the improving description of a rectal-distention pain-related network are important scientific steps to understand the pathophysiology of IBS. Use of relevant comparator groups, such as those with inflammatory bowel disease and psychological disorders, will be essential in expanding this understanding.

Future directions should include efforts to simultaneously assess peripheral and central aspects of the BGA to better understand how these brain findings relate to circumstances in the gut. Coupling brain imaging to measurements of gut motility and permeability, autonomic and endocrine function, individual microbiome, and host transcriptome data would enrich our understanding of the BGA. In addition, joint efforts and collaborations developed to investigate the neurological correlates of IBS, such as the Pain and Interoception Imaging Network[50], and the ENIGMA Consortium[51], will enhance future understanding of the role of the brain-gut axis in patients with IBS.

COMMENTS

Background

Irritable bowel syndrome (IBS) is the most commonly encountered condition by gastroenterologists, yet understanding of disease evolution and treatment interventions remain suboptimal. The "brain-gut axis" (BGA), composed of the enteric nervous system, autonomic nervous system and/or the central nervous system, has been noted as dysregulated in patients with IBS. Neuroimaging is one technique to assess central processing mechanisms in patients with IBS, and may shed light on BGA functioning and its relationship to symptom expression.

Research frontiers

Neuroimaging techniques provide insight as to differences between patients with IBS and healthy volunteers in anatomical measurements of brain structure and connectivity, as well as functional responsiveness of the brain. Neuroimaging modalities in this review include magnetic resonance spectroscopy, diffusion tensor imaging, structural magnetic resonance imaging (MRI), resting state MRI and functional MRI.

Innovations and breakthroughs

The 27 investigations in this review validate prior findings regarding structural and functional differences in brain regions between patients with IBS and healthy volunteers, and reveal new findings related to metabolite concentrations, oscillation patterns, and neurohormones. In addition, an important finding noted across investigations is the confounding influence of patient variables such as sex, psychological factors, and gastrointestinal symptoms, upon the identification of neuroimaging differences between groups.

Applications

Neuroimaging investigations reveal central processing differences between patients with IBS and healthy controls, yet many neuroanatomical findings replicated in the IBS patient population are not specific to the IBS patient population. Further applications should recognize the substantial influence of psychological factors upon the neuroimaging correlates of IBS, use relevant comparator groups, and simultaneously assess peripheral and central aspects of the BGA, in order to optimize understanding as to how brain findings relate to IBS symptomatology.

Terminology

Functional MRI: Measures changes in the oxygen content of blood (through magnetic properties of hemoglobin); increases in oxygenation correlate with increases in neuronal activity; Resting state MRI: Evaluates spontaneous brain activity of intrinsic brain networks, taking place during a wakeful state; Structural MRI: Evaluates cortical thickness as well as white and gray matter volume or density on a global, regional and local scale; Diffusion tensor imaging: Takes advantage of the diffusivity of water to evaluate white matter anatomy and integrity as a function of fractional anisotropy; Magnetic resonance spectroscopy: Measures relative concentrations of metabolites and neurotransmitters in areas of the brain.

Peer-review

In this manuscript, the authors summarize and synthesize current literatures on Neuroimaging the Brain-Gut Axis in patients with IBS.This provided a deep insight into the physiological differences that distinguish patients with IBS from a healthy population.

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