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Pilot Study of Functional Magnetic Resonance Imaging Responses to Somatic Pain Stimuli in Youth With Functional and Inflammatory Gastrointestinal Disease

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ABSTRACT

Background: Brain-gut axis signaling modifies gastrointestinal symptomatology. Altered neural processing of intestinal pain signals involves interoceptive brain regions in adults with functional and inflammatory gastrointestinal disorders. Although these disorders frequently present in childhood, there are no published studies in youth. We determined whether neural processing of somatic pain stimuli differs in adolescents and young adults (AYA) with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), as compared to healthy controls (HC).

Methods: IBS and IBD AYA (16–20 years) underwent anticipated and thermal pain stimuli of low and high intensity on their forearm and simultaneous blood oxygen level–dependent functional magnetic resonance imaging. Data from adult HC were used for comparison. Subjects answered surveys evaluating alexithymia, anxiety, depression, and pain catastrophizing. Group data were compared using linear mixed effects and analysis of variance.

Results: Study groups were similar by sex but not age. Significant group by pain condition interactions were observed in interoceptive brain regions during pain anticipation, and within perceptual brain regions during perceived pain. Higher activation within interoceptive brain regions during anticipated pain was observed in IBS compared with IBD and HC subjects. IBD patients demonstrated increased activation in perceptual brain regions during experienced pain as compared to IBS and HC.

Conclusions: IBS and IBD AYA demonstrate altered neural processing of somatic pain compared with each other and with HC. Our results suggest that neuromodulatory interventions targeting interoceptive brain circuits in IBS and perceptual brain regions in IBD may be effective.

Key Words: functional magnetic resonance imaging, inflammatory bowel disease, interoception, irritable bowel syndrome

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What Is Known

- Functional and inflammatory gastrointestinal disorder patients frequently report pain affecting extraintestinal systems, suggesting abnormal sensitivity beyond the gastrointestinal system.
- Neural processing of extravisceral pain has not been evaluated in patients with gastrointestinal disorders.

What Is New

- Adolescents and young adults with irritable bowel syndrome and inflammatory bowel disease exhibit significantly different neural processing of anticipated and actual somatic pain stimuli compared with each other and with controls.
- Adolescents and young adults with irritable bowel syndrome show increased emotional reactivity and anxiety to anticipated pain, whereas adolescents and young adults with inflammatory bowel disease show increased cognitive control when pain is actually present.

Perception of gastrointestinal (GI) pain varies individually and is modified by signaling between the GI tract and the central nervous system, otherwise known as the brain-gut axis. Studies to date have evaluated pain perception and thresholds in adults with GI disorders and have found that pain perception in these conditions can be functionally altered. Two particular disease entities of interest are inflammatory bowel disease (IBD), typically characterized by periods of GI inflammation accompanied by abdominal pain and diarrhea frequently with blood, and irritable bowel syndrome (IBS), also characterized by abdominal pain and change in bowel movement frequency but in the absence of demonstrated GI inflammation. Chang et al (1) demonstrated differences in perceptual responses to rectosigmoid balloon distension in adults with IBS and IBD, as compared with healthy controls (HC). Specifically, adults with IBS demonstrated a lower balloon inflation threshold for perceived discomfort whereas adults with IBD demonstrated a higher threshold for perceived discomfort as compared across the 3 groups. Zhou et al (2) also demonstrated differences in psychophysical responses to experimental somatic pain stimuli in IBS subjects.

Functional neuroimaging research suggests that IBS pathophysiology may relate to a core impairment in interoception, the neural mechanism by which humans sense the physiologic

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well-being state of the body and through which homeostasis and adaptive emotion processing is achieved (3). Larsson et al (4) demonstrated a correlation between GI tract perceptual responses (to both true and anticipated stimuli) and greater blood oxygen level–dependent signals at brain regions associated with interoception (the cingulate gyrus, insula, and thalamus). Similarly, functional neuroimaging research in adults has demonstrated the importance of the insula in modulating the intrinsic functional connectivity of major networks in the resting brain that is related to IBS symptomatology, with greater connectivity predicting greater intensity of symptoms, particularly chronic visceral pain (5). Visceral placebo analgesia (verbal suggestion of analgesia accompanied by placebo infusion intravenously) has been shown to modulate pain perception in IBS adults (as compared to HC (6) and IBD (7) adults) via enhanced brain activity at interoceptive brain regions (6). Anticipation of visceral pain has also been shown to result in brain activation patterns involving interoceptive brain areas in IBS adult girls (8). Similar studies have yet to be performed in youth with IBS despite the fact that IBS symptoms are prevalent in adolescents (17% of high school students and 8% of middle school students in a community-based sample) (9).

Functional neuroimaging research has also been performed in adult patients with IBD. In general, the IBS population has shown more distinct differences in functional magnetic resonance imaging (fMRI) findings by brain regions (see above) as compared to the IBD population and to HC. Some differences have, however, been noted in patients with IBD as compared with HC. Specifically, attenuation of activation in somatosensory areas during pain and stool sensations with visceral balloon inflation has been seen in the IBD versus healthy control populations (10). Similar to the IBS population, fMRI studies have yet to be performed in youth with IBD despite the fact that IBD commonly presents during the adolescent years (11).

Persons with IBS (12) and IBD (13) frequently have symptoms affecting nonvisceral body systems as well, which suggests that the abnormal sensitivity in these populations extends beyond the GI system. Neural processing of extravisceral or somatic pain stimuli has, however, not been evaluated using fMRI in adult or pediatric patients with functional (IBS) or organic (IBD) GI disease. Nevertheless, fMRI neural processing has been evaluated in HC and in other clinical populations demonstrating pain dysregulation. For example, anorexia nervosa subjects demonstrate an interoceptive brain activation mismatch between anticipation of and objective responses to somatic pain stimuli, suggesting altered integration or perception of body signals (14). The biobehavioral view of pain suggests that pain is an experience with both physiological and psychological factors, and that understanding both these factors is required to effectively understand pain (14). Consistent with this view, the cognitive behavioral theory posits that the degree to which sensory aspects are distressing and/or disabling depends on the way it is interpreted by the patient (eg, pain-related cognitions) and affects the way they cope with or react to it (eg, pain-induced behaviors) (15). Anticipation shapes pain experiences, which are altered in individuals with anxiety (16), depression (17), and chronic pain conditions (18).

To evaluate whether pain processing in youth with GI disorders involves interoceptive pathways in the brain, we evaluated neural responses to somatic pain and its anticipation in adolescents and young adults (AYA) with pain from IBS and IBD in comparison to HC. Because symptomatology in AYA with GI disease is frequently not limited to the GI tract, we evaluated a somatic pain stimulus. We hypothesized that pain processing of a somatic stimulus in AYA with IBS, as compared to HC and AYA with IBD, would result in greater brain activity in interoception-related brain regions, We also hypothesized that pain processing of a somatic stimulus in AYA with IBD, as compared to HC and AYA with IBS, would demonstrate attenuation in pain detection–related brain regions.

METHODS

We performed an evaluation of the neurobiology of pain anticipation and pain processing among AYA with IBS and IBD, and HC. All study subjects completed surveys and an fMRI scan and protocol. This study received local institutional review board approval and informed consent and/or assent was obtained from all subjects.

Subjects

Inclusion criteria for participation included the following: being right-handed, being an adolescent or young adult (AYA) 16–20 years old with IBS or IBD and having abdominal pain during disease exacerbations. IBS participants met Rome III criteria for IBS (19) as confirmed by a pediatric gastroenterologist, whereas IBD participants had been diagnosed by a pediatric gastroenterologist. Subjects with diagnosed psychiatric disorder and/or psychotropic medication exposure within the past 6 months, irremovable ferromagnetic implant, inability to follow protocol, and/or requirement for sedation for MRI were excluded from participation. Data from 10 healthy right-handed young adult HC (age 18–22 years) with no psychiatric history or past or current GI symptoms previously studied as part of a prior neuroimaging study and using the identical study protocol (20) were used for comparison.

Surveys

A battery of surveys and behavior measures assessed baseline emotional and stress states postulated to affect interoception awareness, including alexithymia, anxiety, and depression, in all study subjects. GI symptomatology was measured in IBS and IBD patients; HC had previously reported no GI symptomatology.

Alexithymia

The Toronto Alexithymia Scale-20 (Dr. Greene Taylor, University of Toronto, Canada, 2016) (21) measures difficulty identifying feelings, difficulty describing feelings, and externally orientated thinking and was used to determine patients' levels of alexithymia which has been associated with pain sensitivity.

Anxiety

The Spielberger State-Trait Anxiety Inventory assessed level/severity of baseline anxiety (22). State anxiety refers to anxiety related to temporary stressors, whereas trait anxiety refers to daily anxiety.

Depression

The Beck Depression Inventory-II, a 21-question multiple-choice self-report inventory that measures depressive symptoms (23), was used to screen for and characterize depressive symptoms; higher scores indicate increasingly severe depressive symptoms.

Pain Catastrophizing

Temperament specifically related to pain was measured using an adaptation of Sullivan's Pain Catastrophizing Scale for children (24). Pain catastrophizing has previously been related to perceived pain intensity (25), and pain expression (26).

Gastrointestinal Symptomatology

Disease symptomatology in IBS and IBD is similar. We used the GI Symptoms Rating Scale (27) to assess abdominal pain, dyspepsia, indigestion, and bowel dysfunction (symptoms are rated on a Likert scale of 0 (no symptoms) to 3 (most symptomatic/worst)) and characterize GI symptomatology of IBS and IBD youth in the study.

Experimental Pain Paradigm

A validated pain anticipation paradigm was used (20). Briefly, the paradigm had 2 temporal conditions (anticipation, stimulus) with 3 stimulus conditions for anticipation (cued high pain, low pain, or uninformed pain) and 2 stimulus conditions for stimulus (high pain or low pain). This paradigm was selected to allow evaluation of not only actual stimuli but also the adaptive emotional responses (ie, anxiety) related to anticipation of the stimuli in studied youth. Thermal stimuli, experienced as moderately (6 s; 47.5°C) and mildly (6 s; 45.5°C) painful to the subject, were delivered in a pseudo-random and counterbalanced order through a 9-cm^2 thermode (Medoc TSA-II, Ramat-Yishai, Israel) securely fastened to the subject's left volar forearm. Prior to scanning, subjects were pretested with several nonpainful and painful temperature stimuli to ensure that temperatures were well tolerated.

Postscanner Anxiety and Pain Ratings

To measure the subjective experience of the task, subjects rated anticipatory anxiety, as well as the intensity and unpleasantness of the perceived pain (0 = "no anxiety/pain sensation/unpleasantness" to 10 = "extreme anxiety/pain sensation/unpleasantness") after the scan. Subjects were instructed to provide separate ratings for the low and high pain stimuli.

Functional Magnetic Resonance Imaging Protocol

Two fMRI runs (412 brain volumes/run) sensitive to blood oxygenation level–dependent contrast were collected for each subject using a 3.0-Tesla GE Signa EXCITE scanner (GE Healthcare, Milwaukee, WI) ($T2^*$-weighted echo planar imaging with partial k-space sampling, TR = 1500 ms, TE = 30 ms, flip angle = 80, FOV = 23 cm, 64 × 64 matrix, 30 2.8 mm 1.2 mm gap axial slices) while they performed the paradigm described above. fMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a high-resolution T1-weighted image (FSPGR, TR = 8 ms, TE = 3 ms, TI = 450 ms, flip angle = 12, FOV = 25 cm, 172 1 mm sagittal slices, 256 × 256 matrix) was obtained for anatomical reference.

Statistical Analysis

Demographic and survey data were analyzed according to group assignment (IBS, IBD, or HC) using standard statistical comparison methods. For continuous measures, analysis of variance analyses were used for group comparisons; for noncontinuous measures, Wilcoxon rank-sum test was used for group comparisons. For survey data group comparisons involving control subjects, because demographic analyses demonstrated notable differences in groups by age, age was added as a covariate in analysis of covariance comparison analyses. Analyses were performed using JMP Software version 11 (Cary, NC).

Functional Magnetic Resonance Imaging Statistical Analysis

All imaging data were analyzed with the Analysis of Functional NeuroImages (AFNI) software package (28) as in prior studies (20). Briefly, preprocessed (corrected for: slice-dependent time shifts, interleaved acquisition, rigid body head motion, and despiked (29)) time series data for each individual were analyzed using a multiple regression model corrected for autocorrelation consisting of 3 anticipation-related and 2 stimulus-related regressors. Anticipation-related regressors consisted of anticipation of moderately painful heat stimulation, that is, high pain anticipation; and anticipation of mildly painful heat stimulation, that is, low pain anticipation. Since the uninformed cue did not contribute to our understanding of the specific mechanism of interest, this condition was modeled as regressor of no interest. Stimulus-related regressors consisted of application of moderately painful heat, that is, high pain stimulation; and application of mildly painful heat, that is, low pain stimulation. Six additional regressors were included in the model as nuisance regressors: 1 outlier regressor to account for physiological and scanner noise (ie, the ratio of brain voxels outside of 2SD of the mean at each acquisition), 3 movement regressors to account for residual motion (in the roll, pitch, and yaw directions), and regressors for baseline and linear trends to account for signal drifts. To reduce the false positives induced by cross correlations of the time series data were fit using the AFNI program *3dREMLfit*. A Gaussian filter with a full width-half maximum of 4 mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates.

Voxel-wise percent signal change for high and low pain anticipation and high and low pain were entered into a linear mixed effects model with Group (IBS/IBD/Control) and Condition (low pain/high pain) entered as fixed factors, subjects entered as a random factor, and age as a covariate. Analyses were done with the AFNI function *3dLME.R*, which uses statistical program R (*www.cran.org*) and the NLME library. Results are displayed that showed significant Group by Condition interaction effects for pain anticipation and pain experience. A Monte Carlo simulation (iterations = 10,000) using *AlphaSim* was used to determine that for a search volume within the whole brain a cluster size of 768 mm^3 was required to control for multiple comparisons maintaining an alpha of 0.05. The cluster F values were calculated by averaging the voxel based F values in each cluster. The average percentage signal change was extracted from regions of activation for post-hoc correlational analysis. The between group t tests were performed in the regions that showed significant Group by Condition interactions (the resultant t values are displayed). Spearman's correlation analyses were also performed between extracted percent signal change for Group by Condition interactions during anticipation and stimulation and the Spielberger State-Trait Anxiety Inventory within each patient group. Analyses were performed using JMP Software version 11 (Cary, NC).

RESULTS

Demographic and Clinical Data

Twenty right-handed AYA 16 to 20 years old with IBS (n = 10) and IBD (n = 10) and abdominal pain during disease exacerbations were recruited for participation in the study protocol from a tertiary-care, academic, pediatric gastroenterology center. Ten right-handed adults who were otherwise healthy without GI symptoms underwent the same study protocols. Patient and HC groups did not differ by race (80% vs 50% vs 30% white, IBS vs

IBD vs HC, $P = 0.11$), ethnicity (40% vs 20% vs 20% Hispanic, $P = 0.51$), or sex (80% vs 50% vs 60% female, $P = 0.37$). Age differed among study groups, with IBS (median [interquartile range]: 17 [16, 17] years) and IBD (18 [17, 19] years) groups being on average 3 and 2 years younger than HC (20 [20, 21] years), respectively ($P < 0.0001$).

Anxiety, Depression, Pain, and Gastrointestinal Symptom Data

Survey scores are reported in Table 1. Both IBS and IBD patients demonstrated greater alexithymia symptoms compared to HC ($F = 11.55$, $P < 0.001$). In addition, both IBS and IBD patients reported greater state ($F = 5.18$, $P = 0.01$) and trait anxiety ($F = 8.79$, $P = 0.001$) as compared to HC. Furthermore, measures of depression were higher in IBS patients compared to HC $F = 5.47$, $P = 0.01$) but not between IBD and HC. In contrast, neither pain catastrophizing nor pain ratings during the fMRI protocol differed across groups ($F = 0.06–1.84$; all $P > 0.05$). Anxiety ratings were greater in IBS patients than IBD or HC at rest ($F = 3.48, P < 0.05$) but not during other times during the fMRI protocol. IBS patients reported greater GI symptomatology as compared to IBD patients at the time of study ($P = 0.03$). HC did not report any GI symptoms.

Functional Magnetic Resonance Imaging Data

Heat Pain Anticipation

Figure 1A and Table 2 show significant whole-brain group (IBS/IBD/HC) by condition (high/low pain cue) interaction effects within left anterior cingulate cortex (ACC), left thalamus, left anterior insula (AI), right uncus, and right AI. Further examination of these differences with the between-group *t* tests (Table 3) indicated that patients with IBS demonstrated significantly increased activation within the ACC and bilateral AI as compared to the HC group and increased activation within the ACC, thalamus and right AI but lower activation at the right uncus when compared with the IBD group (T's > 2.04, *P*'s < 0.05). No differences were noted during the anticipation of pain between the IBD and HC groups ($P > 0.05$, all comparisons).

TABLE 1. Survey responses by group

Survey	Irritable Bowel Syndrome	Inflammatory Bowel Disease	Healthy control	P^*
Alexithymia	52 (10)	48 (11)	31 (7)	0.0001
Anxiety (state)	39 (11)	35 (12)	24 (4)	0.007
Anxiety (trait)	38 (10)	40 (11)	27 (5)	0.006
Depression	11 (10)	10 (9)	1 (2)	0.01
Pain catastrophizing	26 (12)	24 (11)	9 (6)	0.001
Gastrointestinal symptoms	0.5 (0.3)	0.2 (0.2)	N/A	0.03
Pain scores during low heat	2 (2)	2.5 (2.5)	1.5 (1.5)	0.90
Pain scores during high heat	6 (2)	6.5 (3)	6 (2)	0.92
Anxiety scores at rest	4.5 (3.7)	1.3 (2.2)	0.1 (0.3)	0.046
Anxiety scores prior to low heat	2 (2)	2.5 (2.5)	1.5 (1.5)	0.85
Anxiety scores prior to high heat	6 (3)	6.5 (2.5)	6.5 (2)	0.81

Results expressed as mean (standard deviation).
*P of analysis of covariance analyses comparing responses by group, controlling for age.

Heat Pain Experience

Figure 1B and Table 2 shows significant whole-brain group (IBS/IBD/HC) by condition (high/low pain stimulus) interaction effects within right superior temporal gyrus, bilateral cerebellum, left lentiform nucleus, right inferior parietal lobule (IPL), bilateral posterior cingulate cortex (PCC), right dorsolateral prefrontal cortex, and left medial frontal gyrus (MFG). Further examination of these differences with the between-group *t* tests (Table 3) indicated that the patients with IBS demonstrated lower activation within bilateral cerebella and right IPL, and higher activation at the left MFG when compared to IBD patients; and significantly lower activation within right superior temporal gyrus, left cerebellum, left lentiform nucleus, right PCC, and right dorsolateral prefrontal cortex when compared with HC. Furthermore, when compared with the HC group, IBD participants demonstrated higher activation within the right IPL and lower activation within bilateral PCC and left MFG.

Functional Magnetic Resonance Imaging Data and Anxiety Data

Because anxiety plays an important role in both functional and organic GI disorders, we examined whether trait anxiety (daily anxiety) measures related to brain activation in our sample. We found that in IBS, trait anxiety correlated positively with brain activation in the ACC during pain anticipation ($\rho = 0.71$, $P = 0.02$) and with brain activation within ventromedial prefrontal during pain stimuli ($\rho = 0.63$, $P < 0.05$). In other words, those IBS subjects with highest trait anxiety showed highest ACC activation during anticipation of pain and highest ventromedial prefrontal cortex (vmPFC) activation during pain experience. In contrast, trait anxiety scores did not correlate with brain activity in patients with IBD. The differences in correlation coefficients between IBS and IBD groups did not meet significance but showed tendency (ACC: $z = 1.1$, $P = 0.14$; VmPFC: $z = 1.4$, $P = 0.07$).

DISCUSSION

This is the first study to demonstrate significant differences in the neural processing of anticipated and actual thermal somatic pain stimuli in AYA with IBS and IBD as compared to each other and with healthy volunteers. In particular, our findings demonstrate a high emotional response to pain anticipation in the anterior cingulate and right anterior insula, brain areas associated with interoception and emotion, among AYA with IBS as compared to IBD AYA and HC. In contrast, AYA with IBD showed anticipatory brain responses similar to that in HC. During pain, AYA with IBD, however, showed more intense neural signaling as compared to AYA with IBS and HC within the right IPL, an area involved in attention to environmental stimuli (30), and more deactivation within the vmPFC, an area within the default mode network, which is active when the brain is at rest or not attending to a given task (31). Taken together, our results are consistent with the idea that AYA with IBS show increased emotional reactivity to the upcoming pain stimuli driven by increased anxiety, while those with IBD do not and may rather show increased cognitive control when pain is actually present. Although prior studies have evaluated GI pain stimuli in adult patients with IBS and IBD as compared to HC (1,7,32), this is the first report to our knowledge to evaluate anticipation and processing of somatic pain stimuli in the setting of IBS and IBD and the first to evaluate pain processing in AYA with IBS and IBD.

Pain is a multidimensional experience that affects overall wellbeing of an individual. Interoception is the integrated neural

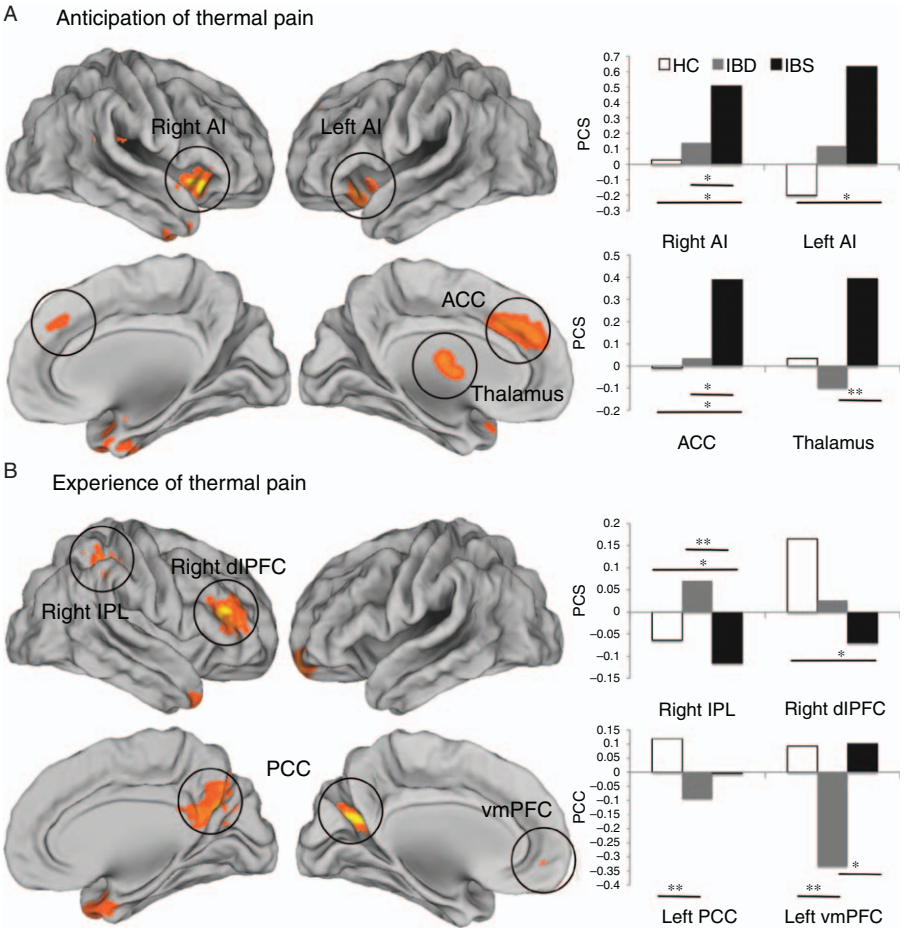

FIGURE 1. Whole brain group (HC, IBD, IBS) by condition (low, high) interaction during anticipation (A) and experience (B) of thermal pain. Bar graphs indicate percentage signal changes (PSC) in the areas that showed significant interaction effects. ACC = anterior cingulate cortex; AI = anterior insula; dlPFC = dorsolateral prefrontal cortex; HC = healthy control; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; IPL = inferior parietal lobule; PCC = posterior cingulate cortex; vmPFC = ventromedial prefrontal cortex. $^{*}P < 0.05$; $^{**}P < 0.01$. See text and Tables 2 and 3 for details.

representation of all aspects of the condition of the body in a system responsible for maintaining homeostasis (33). In the case of gut homeostasis, the intestine provides information to the central nervous system (CNS) via the enteric nervous system (ENS). The CNS in response then communicates to the ENS to affect gut homeostasis. Data to date demonstrate bidirectional effects of brain-gut communications. Recent evidence suggests that interoceptive inputs from the gut, including those generated by intestinal microbes, may influence emotional arousal and affective behaviors (34). Similarly, researchers have demonstrated that psychological distress can produce clinical symptoms and increase disease activity among patients with IBS and IBD (35). Furthermore, activation of the CNS corticotropin-releasing factor system (activated during stress) in the mouse model can alter GI motility and produce clinical symptoms such as diarrhea and also exacerbate existing IBD symptoms and/or induce the flare-up of IBD symptoms (36).

Interoception appears to be processed in the brain primarily within the insular cortex and the ACC (33). Both the insular cortex and the ACC are implicated in perceiving the unpleasantness of pain, generating an emotional response to pain, and controlling our motivational behaviors (37). In this study, we demonstrate a high component of neural signaling in interoceptive areas of the brain (ACC and insular cortices) highly associated with emotion in patients with IBS as compared to both patients with IBD and HC. These areas are also part of the interconnected salience network that shows abnormally tight coupling with the default mode and executive control networks in adolescents with IBS (38). Interestingly, the increase in brain activity in patients with IBS occurred primarily during pain anticipation and not during actual pain stimuli. The increased activation in the MFG in IBS, compared to IBD, patients has been associated with pain anticipation in prior studies and most probably has a cognitive or modulatory, rather than sensory, role (39). The current findings may indicate that actual pain is not required for such altered neural processing but rather anticipation of pain alone may trigger dysregulation of brain signals in areas of the brain involved in interoception.

Other patient populations with classically defined psychiatric illness have demonstrated altered neural signaling and processing in brain regions vital to interoceptive processing in response to pain anticipation or stress induction, including patients with depression (20) and those with eating disorders (40). High activity in interoceptive regions to situational cues, in particular, may be associated with increased disease symptoms (40) and/or increased susceptibility/risk for disease relapse (41). According to Letham's fear-avoidance model, increased activity in these interoceptive brain regions may be a learned response that ultimately leads to an invalid

TABLE 2. Group differences in fMRI signaling in the group (IBS/IBD/HC) by condition (high/low pain cue) interaction [anticipation] and group (IBS/IBD/HC) by condition (high/low pain stimulus) interaction [pain experience]

Brain region	HC	IBD	IBS	IBS > IBD	IBS > HC	IBD > HC
Pain anticipation						
Anterior cingulate cortex	−0.01	0.04	0.39	2.3*	2.6*	NS
Thalamus	0.03	−0.1	0.39	3.0†	NS	NS
L. anterior insula	−0.2	0.12	0.63	NS	2.6*	NS
R. anterior insula	−0.01	0.21	−0.33	2.5*	2.7*	NS
R. uncus	0.03	0.14	0.51	−2.7*	NS	NS
Pain experience						
R. superior temporal gyrus	0.13	−0.08	−0.25	NS	−2.7*	NS
L. cerebellum	0.06	0.07	−0.14	−2.5*	−2.3*	NS
L. lentiform nucleus	0.11	0.01	−0.12	NS	−2.8†	NS
R. inferior parietal lobule	−0.06	0.07	−0.12	−3.2†	NS	2.2*
R. posterior cingulate	0.11	−0.1	−0.11	NS	−2.6*	−2.2*
R. dorsolateral prefrontal	0.17	0.03	−0.07	NS	−2.7*	NS
Cerebellum	−0.03	0.12	−0.12	−2.7*	NS	NS
L. posterior cingulate	0.12	−0.09	−0.01	NS	NS	−3.1†
L. ventromedial prefrontal	0.09	−0.33	0.1	2.4*	NS	−2.8†

HC = healthy control; fMRI = functional magnetic resonance imaging; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome.
*<0.05.
†<0.01.

state and exaggerated pain perception (42). Similarly, Paulus and Stein (43) proposed a role for interoceptive brain regions in triggering anxiety and avoidance behaviors with potential pain amplification. This may be the mechanism for pain amplification in our studied IBS AYA subjects, in whom we found a significant relationship between trait anxiety and increased brain activity in interoceptive regions (ie, ACC). Errors in the processing of interoceptive information may be key in understanding the neural mechanism of IBS and may indicate an exaggerated response to the concept of imminent pain.

Functional MRI findings in patients with IBS implicate the CNS as having a role in the pathogenesis of IBS (44,45). Similarly, our findings support that patients with IBS have a CNS-induced component to their GI disease presentation. Antidepressants and psychological therapies have also been demonstrated as effective treatments for IBS (46). Our findings suggest that neuromodulatory interventions may be helpful to reduce dysfunctional pain signal processing in adolescent patients with IBS. Real-time fMRI feedback studies in adults have already demonstrated that neuromodulation of brain signaling at the ACC can effectively reduce pain severity perception (47), and neuromodulatory interventions including mindfulness training have been shown to modulate ACC and insula signaling (37).

In regards to pain processing in IBD, the only region that showed significantly higher pain activation in IBD compared to IBS and HC groups was IPL, an area important in cognitive control of emotion (48) and pain (49). The IPL is part of the frontoparietal control network that plays an important role in cognitive pain modulation (7). Activation at the IPL has been associated with reduced pain sensations when subjects are prompted incorrectly to anticipate a particular thermal pain stimulus (48). Interestingly, IBD also showed more deactivation within medial prefrontal cortex (mPFC), compared to both groups and more deactivation within the PCC compared to the controls. Both the mPFC and PCC areas lie within the Default Mode Network (DMN), thought to be implicated in self-referential cognitive processing, self-awareness and self-monitoring (31). The mPFC is involved in pain perception during spontaneous pain changes in patients with chronic back pain patients, with high-frequency brain activity oscillations correlating positively with pain ratings (50). Taken together, our findings suggest that cognitive diversion techniques may be the mechanism used in IBD to downregulate or modulate the pain experience. Our

TABLE 3. Group (IBS/IBD/HC) by condition (high/low pain cue) interaction [anticipation] and group (IBS/IBD/HC) by condition (high/low pain stimulus) interaction [pain experience] within the whole brain analysis

Brain Region	Volume, mm^3	Talairach coordinates			F
		X	Y	Z	
Pain anticipation					
L. anterior cingulate cortex	4288	−7	31	36	5.0
L. Thalamus	1408	−4	−13	12	4.6
L. anterior insula	1152	−35	19	−12	5.2
R. anterior insula	896	33	18	−5	5.4
R. Uncus	1024	35	1	−29	5.3
Pain experience					
R. superior temporal gyrus	1984	32	10	−32	4.6
L. Cerebellum	1984	−13	−59	−25	4.8
L. lentiform nucleus	1792	−29	−9	2	4.9
R. inferior parietal lobule	1408	39	−40	45	5.2
R. posterior cingulate cortex	1344	8	−61	26	4.7
R. dorsolateral prefrontal cortex	1216	38	31	19	4.9
Cerebellum	1152	1	−42	−14	4.5
L. posterior cingulate cortex	1024	−23	−63	20	5.2
L. ventromedial prefrontal cortex	768	−18	51	−4	4.7

HC = healthy control; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome.

data demonstrate similar activation patterns of brain regions in patients with IBS and IBD as others have demonstrated in adult patients with IBS and IBD in response to aversive visceral stimuli (32). These findings suggest that altered processing of pain signals is not isolated to the inputs or sensations from the intestine in patients with IBS and IBD, but affects global sensory inputs as well.

This study has several limitations. First, as our study is a cross-sectional evaluation, we cannot assign causation to our findings. We acknowledge the small sample size, which may thus not adequately represent fully the studied populations and limit our ability to fully control for multiple confounders. In addition, we acknowledge the slight discrepancy in age distribution between the control and study groups in the article. We controlled for these differences in all of the performed analyses and demonstrate notable differences in the neural processing and anticipation of somatic pain signals between AYA with IBS and IBD, as well as in contrast with HC. Although the age contribution cannot be completely ruled out, the insula cortex, an epicenter of interoceptive processing, does not mature until the mid third decade of life (20 s) (8,10). Therefore, we are confident that the observed differences were not influenced by slight age differences between the groups in our study. Further study is needed to determine whether these differential responses ultimately translate into GI symptomatology as implied. In addition, whether these demonstrated responses in adolescence and young adulthood ultimately contribute to changes in adult neuroanatomy and function remains to be fully evaluated. Finally, in our prior work, adults were able to undergo the fMRI protocol without increased anxiety or other adverse reactions. Similarly, IBS and IBD AYA did not express any differences in anxiety scores during the fMRI protocol as compared with controls. Also, standardized somatic pain stimuli were determined through preliminary pain tolerance screening rather than based on subject-determined thresholds. Nevertheless, every subject was pretested before the MRI scan to ensure similar subjective pain ratings to chosen temperature stimulations. The groups did not differ in pain experienced (Table 1) during either low or high pain stimulation conditions.

CONCLUSIONS

We demonstrate altered neural processing of somatic pain signals in AYA with both IBS and IBD in comparison to each other and to HC. Specifically, the IBS group showed significantly greater activation in brain regions associated with interoception and decreased activation in brain regions associated with pain signal processing as compared with IBD and HC, whereas the IBD group demonstrated altered activation in brain pain processing regions in comparison with HC. Disorder-specific neuromodulatory interventions specifically targeting interoceptive brain areas may thus be effective for pain control in AYA with IBS, whereas interventions targeting pain processing regions may be helpful in AYA with IBD.

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