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Brain functional connectivity is associated with visceral sensitivity in women with Irritable Bowel Syndrome

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ABSTRACT

Increased perception of visceral stimuli is a key feature of Irritable Bowel Syndrome (IBS). While altered resting-state functional connectivity (rsFC) has been also reported in IBS, the relationship between visceral hypersensitivity and aberrant rsFC is unknown. We therefore assessed rsFC within the salience, sensorimotor and default mode networks in patients with and without visceral hypersensitivity and in healthy controls (HCs).

An exploratory resting-state functional magnetic resonance imaging study was performed in 41 women with IBS and 20 HCs. Group independent component analysis was used to derive intrinsic brain networks. Rectal thresholds were determined and patients were subdivided into groups with increased (hypersensitive IBS, N = 21) or normal (normosensitive IBS, N = 20) visceral sensitivity. Between-group comparisons of rsFC were carried-out using region-of-interest analyses and peak rsFC values were extracted for correlational analyses.

Relative to normosensitive IBS, hypersensitive patients showed increased positive rsFC of pregenual anterior cingulate cortex and thalamus within the salience network and of posterior insula within the sensorimotor network. When compared to both hypersensitive IBS and HCs, normosensitive IBS showed decreased positive rsFC of amygdala and decreased negative rsFC in dorsal anterior insula within the DMN. DMN and sensorimotor network rsFC were associated with rectal perception thresholds, and rsFC in posterior insula was correlated with reported symptom severity in IBS.

Our exploratory findings suggest that visceral sensitivity in IBS is related to changes in FC within resting-state networks associated with interoception, salience and sensory processing. These alterations may play an important role in hypervigilance and hyperalgesia in IBS.

1. Introduction

Irritable Bowel Syndrome (IBS) is a chronic visceral pain syndrome defined by recurrent abdominal pain associated with altered bowel habits with no detectable organic causes. In the absence of a reliable biomarker (Drossman, 2016; Enck et al., 2016; Longstreth et al., 2006), current concepts support an important role of enhanced visceral perception sensitivity ("visceral hypersensitivity") within a dysfunctional brain-gut axis (Drossman, 2016; Enck et al., 2016; Farmer and Aziz, 2013; Mayer et al., 2015b). Functional magnetic resonance imaging (fMRI) studies have made a substantial contribution to elucidating central mechanisms involved in normal and altered processing of visceral stimuli, including the perception of visceral pain. They have provided important insights into functional alterations in response to experimentally induced pain in IBS, involving brain regions of visceral afferent processing, emotional arousal and endogenous pain modulation (Tillisch et al., 2011). The investigation of spontaneous, stimulus-independent brain activation and connectivity of intrinsic brain networks by resting-state fMRI (rsfMRI) extends knowledge derived from studies involving experimental pain models (Napadow and Harris, 2014). Existing rsfMRI studies in functional gastrointestinal disorders (FGIDs) support altered functional connectivity (FC), with most consistently reported alterations in the default mode network (DMN), salience and sensorimotor networks (Lee et al., 2016; Mayer et al., 2015a).

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Although visceral hypersensitivity is considered a key feature in the pathophysiology of FGIDs (Azpiroz et al., 2007; Keszthelyi et al., 2012), a significant proportion of patients have visceral pain thresholds within the normal range (Bouin et al., 2002; Lee et al., 2006; Sabate et al., 2008). Despite the absence of perceptual hypersensitivity to rectal distension, these patients exhibit chronic gastrointestinal (GI) symptoms and demonstrate alterations in brain responses to experimental pain stimuli (Elsenbruch et al., 2010a, 2010b; Icenhour et al., 2015). Even though there is evidence suggesting differences between hypersensitive and normosensitive patients in response to painful stimuli (Larsson et al., 2012; Van Oudenhove et al., 2010), the relation between altered FC of brain networks and visceral sensitivity remains unknown. Using a data-driven approach (independent component analysis; ICA), the current exploratory rsfMRI study aimed to address differences within the DMN, salience and sensorimotor networks, as the intrinsic brain networks most consistently exhibiting alterations in IBS, in a sample of hyper- and normosensitive patients and healthy controls (HCs). IBS subgroups were subdivided based on sensory thresholding performed subsequent to rsfMRI by means of rectal distensions with a balloon catheter placed before scanning. We hypothesized alterations in FC within these networks to be related to visceral sensitivity in IBS, as evidenced by distinct changes in both hyper- and normosensitive patients. Specifically, we tested for group differences in FC in insular and cingulate subregions, thalamus, and amygdala, as brain regions consistently reported to be activated by visceral stimulation (Tillisch et al., 2011). In addition, we addressed associations between changes in FC, visceral sensitivity, GI symptom severity and emotional disturbances in IBS.

2. Materials and methods

2.1. Participants

In total, 44 right-handed female IBS patients fulfilling Rome III diagnostic criteria were referred from primary care units and 20 age-matched, right-handed female HCs were recruited by local advertisement to participate in this fMRI study. Participants underwent a screening procedure including a standard clinical examination by a trained gastroenterologist to exclude organic GI diseases. In all patient, standard laboratory examination (minimum: hemoglobin, white blood cell count, C-reactive protein) and clinical examinations were performed before inclusion. Celiac disease was excluded by transglutaminase antibodies and f-calprotectin was used to screen for inflammatory bowel disease (IBD). Patients kept a gastrointestinal symptom diary for 2 weeks and were evaluated in terms of GI symptoms and alarm symptoms. Additional specific testing was performed when appropriate, e.g. colonoscopy when considered relevant for the exclusion of microscopic colitis. Lactose intolerance and bile acid malabsorption were excluded when appropriate. Further exclusion criteria were metabolic, neurological or severe psychiatric disorders, intake of nicotine or centrally acting medication, claustrophobia, pacemaker, large tattoos and metal implants in the brain. In HCs, a medical history of GI disturbances or complaints was exclusionary. All participants gave informed written consent and the Regional Research Committee for Ethical Issues at the Faculty of Health Sciences, Linköping, Sweden, approved the study. HCs received a monetary compensation of 1000 Swedish kronor (approx. 105 €).

2.2. Study protocol

2.2.1. Resting-state fMRI data acquisition

All participants were tested between 8 a.m. and 5 p.m. and temporal overlap with menses was avoided. Participants were asked to cease medication and avoid alcohol consumption for at least 24 h and fast for at least 4 h before the experiment. After arrival, a rectal balloon catheter consisting of a noncompliant polyethylene bag (maximal volume 520 mL) attached to a polyethylene tube was placed according to a standard clinical procedure. Balloon placement before scanning was performed for patient convenience, avoiding effects of negative expectations regarding the placement procedure. Participants were given several minutes to habituate to the catheter before they were placed in the MR scanner and underwent a 5-minute adjustment phase to the scanner environment, during which no scanning was performed. Subsequent to this habituation phase, an eyes closed resting-state functional brain scan was acquired. MRI scanning was performed on a Philips Achieva 1.5 T whole-body MR scanner (Philips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil, located at the Center of Medical Image Science and Visualization at the Linköping University Hospital in Linköping, Sweden. A blood oxygen level dependent (BOLD) sensitive gradient echo, echo planar imaging sequence that effectively covered the whole brain was applied with the following acquisition parameters employed: Repetition time (TR) = 3 s; Echo time (TE) = 40 ms; flip angle (FA) = 90°; voxel size 3x3x3 mm^3; slice thickness = 3 mm; gap = 0.5 mm; number of slices = 35; scan time = 10 min. During scanning, participants were instructed to lie still with their eyes closed. Data from three IBS patients were excluded from further analyses due to intolerance of the MRI procedure (i.e. claustrophobia), resulting in a final sample of 41 IBS patients and 20 HCs, who reported no adverse effects of the fMRI measurement or balloon placement based on self-report, as assessed at the conclusion of rsfMRI. After the fMRI scan, participants were prompted to rate intensity and unpleasantness of currently experienced GI symptoms on scales ranging from 0 to 10 with 0 indicating no intensity/unpleasantness and 10 defined as very high intensity/unpleasantness.

2.2.2. Determination of perceptual thresholds

Following rsfMRI, visceral perceptual thresholds as measures of visceral sensitivity were determined with an electronic barostat (Dual Drive Barostat, Distender series II; G & J Electronics Inc., Toronto, ON, Canada). Specifically, intermittent phasic isobaric rectal balloon distensions of 30 seconds durations were delivered, and visceral sensitivity was assessed using an ascending method of limits with pressure increments of 5 mm Hg, as previously described (Larsson et al., 2012). Subjects were prompted to rate each sensation on a 4-point scale labeled 0 = no sensation, 1 = first/some sensation, 2 = urge to defecate and 3 = maximal tolerable distension pressure. Based on the lower range of maximal tolerable pressures in HC (mean pressure 55 mm Hg; range: 40–70 mm Hg), IBS patients were classified as either normosensitive (N = 20, mean pressure 47.75 mm Hg; range: 40–70 mm Hg) or hypersensitive (N = 21, mean pressure 29.52 mm Hg; range: 20–35 mm Hg) with no overlap in maximal tolerable distension pressures between hypersensitive IBS and HCs. This classification procedure was previously implemented in the few existing studies comparing hypersensitive and normosensitive IBS (Kuiken et al., 2005; Larsson et al., 2012). The lower range of maximal tolerable pressures in HCs is well in accordance with previously published maximal tolerable pressure volumes from visceral sensitivity testing assessed with comparable methodology in healthy women (Sloots et al., 2000).

Subsequent to rsfMRI and the thresholding procedure, a subset of participants included in the current study underwent an fMRI paradigm to investigate group-differences in cerebral responses to the expectation and presentation of standardized rectal distensions. Data from this fMRI study have previously been published (Larsson et al., 2012) and are not addressed here.

2.3. Questionnaires

2.3.1. Hospital Anxiety and Depression Scale (HADS)

In all participants, the Hospital Anxiety and Depression Scale (HADS) was used to evaluate levels of anxiety and depression (Zigmond and Snaith, 1983). HADS consists of seven items addressing states of anxiety and depression, respectively, which are scored on a 4-point