

## Sex differences in emotion-related cognitive processes in irritable bowel syndrome and healthy control subjects

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### ABSTRACT

Greater responsiveness of emotional arousal circuits in relation to delivered visceral pain has been implicated as underlying central pain amplification in irritable bowel syndrome (IBS), with female subjects showing greater responses than male subjects. Functional magnetic resonance imaging was used to measure neural responses to an emotion recognition paradigm, using faces expressing negative emotions (fear and anger). Sex and disease differences in the connectivity of affective and modulatory cortical circuits were studied in 47 IBS (27 premenopausal female subjects) and 67 healthy control subjects (HCs; 38 premenopausal female subjects). Male subjects (IBS + HC) showed greater overall brain responses to stimuli than female subjects in prefrontal cortex, insula, and amygdala. Effective connectivity analyses identified major sex- and disease-related differences in the functioning of brain networks related to prefrontal regions, cingulate, insula, and amygdala. Male subjects had stronger connectivity between anterior cingulate subregions, amygdala, and insula, whereas female subjects had stronger connectivity to and from the prefrontal modulatory regions (medial/dorsolateral cortex). Male IBS subjects demonstrate greater engagement of cortical and affect-related brain circuitry compared to male control subjects and female subjects, when viewing faces depicting emotions previously shown to elicit greater behavioral and brain responses in male subjects.

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## 1. Introduction

Sex-related differences in the structure and function of the human brain [36] have paralleled sex-specific prevalence rates of chronic pain disorders [19,47,54]. Sex-based differences in the brain's response to symptom-related affective and cognitive stimuli may be important for understanding the pathophysiology of these disorders in terms of increased susceptibility to develop these disorders and in order to develop more effective individualized therapies [67].

Irritable bowel syndrome (IBS) occurs with a slightly greater prevalence in female subjects [10,19,43,50], and sex-related differences in visceral perception, autonomic nervous system, and brain responses to visceral stimuli have been reported [11,39]. Male subjects show greater sympathetic nervous system and hypothalamic-pituitary-adrenal axis responses to certain types of stress, whereas female subjects show reduced vagal tone and greater visceral hypersensitivity [11,70]. Brain imaging studies in rodents [78] and in IBS subjects [44–46,73,77] during aversive visceral stimulation, and expectation of such stimuli, demonstrate greater engagement of cortical regions (insula [INS] and dorsal prefrontal cortex [PFC]) in male subjects, and greater engagement of affective brain regions and related circuits in female subjects (amygdala [AMYG], subgenual cingulate cortex [sgACC]) [40,53]. These findings suggest that in response to gut- (and disease-) related stimuli, IBS subjects show sex-related differences in brain activation and functional connectivity.

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In response to emotion-related stimuli (including faces, images, words, odors, music), female subjects generally show greater brain activation related to emotions of sadness, disgust, and unpleasantness [67], whereas men demonstrate greater neural responses to emotions such as anger, fear, and guilt [29,67]. Differences in brain responses to the viewing of faces expressing different emotions have been used to measure differences in the engagement of emotion-related brain circuits and their cortical modulation [13,20,22,58,66], as well as disease- [18,56,63,66,76] and sex-related [21,29,36,67] differences in these circuits. Although differences in amygdala responsiveness and cortical modulation of such responses when viewing fear-related faces have been demonstrated, this paradigm is not associated with changes in subjective emotions or autonomic responses [15,23].

In the current study, we used the paradigm of viewing negative affective (fear and anger) and neutral faces to test sex- and IBS-related differences in brain response associated with cognitive processes, ie, processing negative emotions. We studied a large sample of male and predominantly premenopausal female IBS subjects and matched healthy control subjects (HCs) by monitoring brain responses to negative facial emotions (fear and anger) in the NimStim paradigm [71], which is a variation on the Ekman faces [16,71]. We aimed to test the following hypotheses. (1) Greater brain responses in affective regions and less recruitment of prefrontal inhibitory regions will be observed in IBS subjects compared to HCs, in male compared to female subjects, in male IBS compared to female IBS patients, and in male HCs compared to female HCs. (2) Greater regional brain activation by the emotional faces paradigm will be accompanied by changes in the effective connectivity of the emotion-related circuit and its cortical modulatory input.

## 2. Materials and methods

### 2.1. Participants

This study was approved by the institutional review board of the University of California, Los Angeles. All subjects provided written informed consent to participate. IBS subjects were recruited through the UCLA Digestive Disease Clinic and from community advertisements. The diagnosis of IBS was confirmed using Rome III [14] criteria during a clinical examination by a gastroenterologist or nurse practitioner experienced in functional gastrointestinal (GI) disorders. IBS is defined as recurrent abdominal pain or discomfort for at least 3 days/month in the last 3 months and is associated with 2 or more of the following: (1) improvement in defecation, (2) onset associated with a change in frequency of stool, (3) onset associated with a change in form (appearance) of stool. HCs were recruited by advertisement and screened via medical examination for absence of functional pain disorders. Inclusion criteria for all subjects included the absence of current or past psychiatric illness or substance abuse disorder and the absence of major medical or neurological conditions. No subjects were taking medications for 30 days before scanning. Fourteen healthy control subjects from another onsite imaging study took a placebo medication on the day of scanning. To determine whether the HC subjects taking placebo could be combined with the HC subjects not taking placebo, an independent sample *t* test was applied using Statistical Parametric Mapping V8 [51] and indicated no statistically significant differences in brain response to stimuli on the faces paradigm between the 2 groups, supporting the combination of the 2 groups to create a larger sample size of HC subjects.

### 2.2. Questionnaires

Subjects completed the UCLA Bowel Symptom Questionnaire [49] to measure symptom severity, anxiety and depression were

measured using the Hospital Anxiety and Depression (HAD) measure [81]. For female subjects, menopause status was assessed by a self-report question that categorized the subjects as either premenopausal or postmenopausal, and the majority of the studies were done during the follicular phase of the menstrual cycle. The majority of female subjects in the study (82%) were not taking any oral contraceptives.

### 2.3. Functional magnetic resonance imaging (fMRI) data acquisition

fMRI was performed using a 3.0-T MRI scanner (Siemens Trio; Siemens, Erlangen, Germany). A high-resolution structural image was acquired from each subject with a magnetization-prepared rapid acquisition gradient-echo sequence, repetition time (TR) = 2300 ms, echo time (TE) = 2.85 ms, 256 slices, 160 × 240 matrix, voxel size 3 mm. Functional blood oxygen-level dependent images were acquired (TR = 3000 ms, TE = 28 ms, flip angle = 90°, 38 slices, slice thickness = 3 mm) while subjects completed 2 runs of the emotional faces tasks. Stimuli were presented via MRI-compatible goggles using Superlab 4.0 software (Cedrus Corp, San Pedro, CA). Subjects responded using an MRI-compatible button box by pressing 1 of 2 buttons with the right hand.

### 2.4. fMRI imaging task: faces paradigm

One of the most commonly used experimental paradigms for fMRI studies has been the viewing of images with negatively valenced facial expressions [24,27,31]. Paradigms using negative emotional facial expressions also have been used in several imaging genetics studies demonstrating increased hyperresponsiveness of emotion-related networks (including the amygdala) in healthy control subjects with increased harm avoidance and SERT gene polymorphisms [25,26,34], and within several psychiatric disorders including posttraumatic stress disorder [18,63], autism [76], trait anxiety [56,66], and Parkinson disease [61].

During this fMRI study, brain responses to the NimStim Emotional Faces Viewing task [71] were measured. During matching emotions (ME), subjects viewed a target face depicting an angry or fearful expression and were asked to select 1 of 2 other faces that expressed the same emotion. During matching form (MF), a condition controlling for the sensory-motor aspects of the ME task, subjects viewed a target circular shape (approximately the same size as a human face) and were asked to select 1 of 2 other shapes that best matched the target. Participants also viewed the same target faces as in the matching condition, but had to judge which of 2 linguistic labels, such as angry or afraid, best described the emotion (identifying emotion [IDE]). As a control task, the subjects viewed the same target faces, but labeled the faces based on their gender, either male or female, and not on affect (identifying gender [IDG]). We did not analyze the results of the linguistic labeling task in this article. Stimuli were shown with randomized sequences counterbalanced across 2 runs. Each condition was presented as a block of 6 images, with each image presented for 3 s, with a total block length of 18 s. In each run, each condition (ie, match forms) was randomly presented. An instruction cue was presented for 3 s prior to each block, and a rest period of 6 s followed each block. Each run began with a 30-s anticipatory baseline.

### 2.5. Data analysis: image processing and data analysis

#### 2.5.1. Preprocessing

The first 2 volumes were discarded to allow for stabilization of the magnetic field. The remaining functional images were slice-time and motion corrected, spatially normalized to the MNI (Montreal Neurologic Institute) template, and spatially smoothed with an 8 mm<sup>3</sup> Gaussian kernel using SPM8 (Wellcome Department of

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