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Reduced functional connectivity between the hypothalamus and high-order cortical regions in adolescent patients with irritable bowel syndrome

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Abstract

The hypothalamus plays a critical role in maintaining visceral homeostasis. Altered hypothalamus activation has been implicated in functional gastrointestinal disorders, including irritable bowel syndrome (IBS). One important aspect of homeostatic regulation is the cortical modulation of limbic and paralimbic subsystems, including the hypothalamus, which in turn affects the descending regulatory processes mediating visceral homeostasis. Using neuroimaging, we evaluated hypothalamus functional connectivity in adolescent IBS patients and age-matched healthy controls who received rectal distension stimulations. More extensive hypothalamus connectivity was observed in liminal than subliminal condition in controls, but not in IBS patients. Compared with controls, IBS patients showed significantly reduced hypothalamus connectivity in the bilateral prefrontal cortices, supplementary motor and premotor areas, bilateral sensorimotor cortex, and limbic subareas, which are specifically involved in homeostatic regulation. The findings support the generalized homeostatic regulation model that reduced cortical and limbic modulations of hypothalamus functioning underlies disrupted visceral homeostasis in IBS patients.

Keywords

Irritable bowel syndrome; Functional magnetic resonance imaging (fMRI); Homeostatic regulation; Hypothalamus functional connectivity

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Introduction

Functional imaging studies have primarily focused on detecting neural signatures of visceral pain and visceral hypersensitivity in the central nervous system (CNS) in patients with irritable bowel syndrome (IBS). Viewed in a more comprehensive conceptual framework, IBS symptoms also can be characterized by dysfunctions in a generalized model of visceral homeostatic regulation within the brain-gut axis, regulating not only physiological conditions of the viscera, but also the associated emotional and motivational contents [1].

The hypothalamus plays a critical role in regulating visceral homeostasis through its intimate connections with the autonomic nervous system, neuroendocrine system, and limbic system [2]. The hypothalamus receives direct sensory inputs from the smell, taste, visual, and somatosensory systems, as well as inputs from the forebrain areas including the thalamus; hippocampus; amygdala; and cingulate, insular and frontal cortices [3]. Also, the hypothalamus is considered the major control center of the visceral motor system through its connections with the nuclei in the brainstem that mediate visceral reflexes and with the preganglionic neurons of the sympathetic and parasympathetic nervous systems [4].

One important aspect of visceral homeostasis regulation is the cortical modulation of homeostatic afferent input to the CNS [1]. Prefrontal, limbic, paralimbic, and sensory and motor cortices all can exert modulatory influences on the gains of autonomic reflexes. Of these, the hypothalamus functions as one important mediator for the cortical modulation of visceral homeostasis with its bidirectional ascending and descending pathways. Specifically, a set of prefrontal regions modulates activities in limbic and paralimbic regions, subregions of the anterior cingulate cortex (ACC), and the hypothalamus, which in turn regulate activities of descending inhibitory and facilitatory pathways through the periaqueductal gray (PAG) and pontomedullary nuclei [1, 5]. The interactions in these corticolimbic pontine networks are thought to mediate the cognitive and emotional aspects of homeostatic afferents, including visceral pain and discomfort.

The goal of this study was to evaluate, using functional imaging, alterations of hypothalamus functional connectivity in adolescent IBS patients. We hypothesized that IBS patients are characterized by reduced hypothalamus functional connectivity with cortical and limbic structures that are specifically involved in homeostatic regulation, reflecting a lack of cortical modulatory effects on the hypothalamus as a mechanism of the failure of maintaining visceral homeostasis in IBS.

Methods

Study participants included nine adolescent IBS patients aged 12–17 years (five females and four males; mean age, 14.9; standard deviation [SD], 1.9) and eight age-matched healthy volunteers (controls) aged 12–16 years (three females and five males; mean age, 14.6; SD, 1.6). All patients meet Rome III criteria for the diagnosis of IBS. Controls were screened for functional gastrointestinal disorders and any painful medical condition. Participants with major clinical depression, anxiety, claustrophobia, or fear of loud sounds also were excluded. Two scans were performed during each of the subliminal and liminal non-painful

rectal distension stimulations administered using a commercially available computer-controlled barostat. The average balloon pressures that elicited subliminal and liminal stimulation were at 15 ± 4 mmHg and 24 ± 4 mmHg for IBS patients, and 16 ± 6 mmHg and 26 ± 5 mmHg for controls, respectively. In order to reduce anxiety, each participant was accompanied to the scanner by a parent(s) and physician(s) and a mock scan was performed prior to the research scan. No participant reported feeling of pain during liminal stimulation. Each fMRI run consisted of four repeating cycles, with each cycle comprising a 15-second pressure and a 25-second rest (Fig. 1A). For detailed imaging data preprocessing procedures, we refer the reader to our recent publication [6], which used the same data set. The hypothalamus was manually identified in high spatial-resolution anatomical images of each participant as the seed region for a functional connectivity analysis. Functional connectivity was assessed by Pearson cross-correlation of the average blood-oxygen-level dependent (BOLD) time series of voxels in the hypothalamus with the rest of brain voxels. Group connectivity maps and condition comparisons between IBS and control groups were determined by one and two-sample *t*-tests with correction of multiple comparisons using a probability and cluster thresholding technique (*AlphaSim* in AFNI; a minimum cluster threshold of 179 voxels to suppress false-positive occurrence).

Results

The control and IBS groups showed distinct spatial patterns of hypothalamus functional connectivity in subliminal and liminal rectal distension conditions. Specifically, controls showed extensive connections with multiple cortical areas while IBS patients did not.

During subliminal stimulation, the hypothalamus showed common connections in both groups with the ACC (more in the pregenual ACC [pACC] in IBS patients and dorsal ACC [dACC] in controls), bilateral insula, middle and superior temporal gyrus, amygdala, thalamus, hippocampus, parahippocampal cortex, uncus; basal ganglion structures including the putamen, globus pallidus and caudate; and cerebellum subregions (Figs. 1A and 1B). IBS patients also showed connections in scattered areas in the left inferior and middle frontal gyrus, cuneus, and the middle and superior temporal gyrus (Fig. 1B). In contrast, controls showed additional connectivity with a large set of cortical regions in the bilateral inferior and middle frontal gyrus, dACC, bilateral sensorimotor areas, supplemental motor area (SMA), premotor cortex, inferior and superior posterior parietal lobe, angular and supramarginal gyrus, cuneus, and part of the middle cingulate cortex (MCC) (Fig. 1A). In both groups, prominent hypothalamus connections with the midbrain structures, PAG, parabrachial nucleus, and other subareas of the pons were observed.

During liminal stimulation, hypothalamus connectivity involved nearly the identical set of neural structures as those during subliminal stimulation in each group (Figs. 1C and 1D). Compared with subliminal stimulation, there was a prominent increase in the extent and magnitude of hypothalamus connectivity in all involved cortical regions in controls (Fig. 1C) but not in IBS patients. IBS patients, however, showed hypothalamus connections in clustered areas of the angular and supramarginal gyrus; moreover, connections in the ACC expanded beyond the pACC, as identified during subliminal stimulation to include the dACC (Fig. 1D).

Group comparisons revealed a trend of between-group differences similar to those observed in individual group maps. Compared with controls, IBS patients showed reduced hypothalamus connectivity in the subliminal condition in the bilateral prefrontal and sensorimotor cortices; SMA; hippocampus; parahippocampal cortex; uncus; amygdala; angular and supramarginal gyrus; part of the MCC; and scattered areas in the parietal, temporal areas, and pons (Fig. 2A; see Supplemental Digital Content 1 for a table of region-specific group differences of hypothalamus functional connectivity). In the liminal condition, IBS patients showed reduced hypothalamus connectivity in the same set of brain structures as those during subliminal stimulation, but with the extent of areas and magnitude of reduction increased prominently (Fig. 2B; see Supplemental Digital Content 2 for a table of region-specific group differences of hypothalamus functional connectivity). The results indicate that reduced hypothalamus connectivity exhibits in a consistent set of brain structures in IBS patients, with the extent of areas and magnitude of reduction enlarged during liminal stimulation.

Discussion

Within the brain-gut axis, the hypothalamus plays an important role in regulating viscera functions and maintaining homeostasis, and its function in turn is modulated by higher-order cortical and limbic regions [2]. Here we examined alterations of hypothalamus functional connectivity in adolescent IBS patients, hypothesizing that IBS is accompanied by reduced hypothalamus connectivity with the cortical and limbic regions which are specifically involved in visceral homeostatic regulation. In the context of the proposed homeostatic afferent processing network model [1], we considered reduced hypothalamus connectivity with the associated cortical and limbic regions a manifestation of disrupted cortical modulation of hypothalamus functioning, which may impact the descending regulatory processes important for visceral homeostasis and may explain, in part, the disrupted visceral homeostasis in IBS patients [1].

One major difference of hypothalamus functional connectivity between healthy controls and IBS patients was observed in large brain areas involved in sensory and motor functions, including the bilateral sensorimotor cortex, SMA, and premotor cortex. Hypothalamus connections with sensorimotor systems play at least two important roles essential to visceral homeostatic regulation. First, activities in the somatosensory cortices (S1, S2), as well as the insular cortex, are intimately involved in the sensory-discriminative aspect of pain and visceral sensation processing, including, for example, analysis of the location, intensity, and duration of the stimulus [7–9]. Second, hypothalamus connections with motor-function-related brain areas would be required for the hypothalamus to mount a motor response triggered by visceral stimuli, irrespective of the intensity of the stimulus. The response to subconscious or conscious perception involves motor planning and anticipation by the premotor cortex, facilitation of complex movements by the SMA, and actual execution of motor plans by the primary motor cortex. The motor cortices have projections that indirectly influence autonomic control of visceromotor functions [10]. A recent study showed that sensory/motor cortices exhibit abnormal mean diffusivity of white matter organization in IBS patients [11]. Reduced hypothalamus connectivity was also found in IBS patients in the supramarginal gyrus, which is specialized for multimodal association and sensory

integration [12]. Hypothalamus connectivity with this specific region likely reflects the need of integrating visceral afferents with contextual information to provide an overall sense of intrusion and threat to the body during homeostatic regulation. Our study suggests that such a connection may be disrupted in IBS patients.

Hypothalamus connectivity in IBS patients was also reduced prominently in the bilateral dorsolateral prefrontal cortex (DPFC), hippocampus, parahippocampal cortex, uncus, amygdala, and part of the MCC, especially during liminal stimulation. These neural structures are collectively involved in the cognitive-evaluative and affective-motivational components of CNS processing of visceral sensation [8, 9]. Sensory information from the viscera needs to be integrated with contextual information and memory to provide cognitive mediation for homeostatic regulation. This process requires the involvement of the bilateral DPFC, which regulates attention, working memory, executive controls [13], as well as the hippocampus, parahippocampal cortex, and uncus, which are essential in integrating visceral afferent information with past experiences. Moreover, the emotional response or valence can never be separated from the CNS processing of pain and visceral sensation. With respect to the affective-motivational component, the amygdala and hippocampus constitute the major network nodes in the emotional arousal network [14, 15], together with the involvement of the hypothalamus [16]. The MCC with its reciprocal connections with the lateral and medial DPFC and SMA mediates the motivational aspect of visceral sensation and response selection [17]. Our findings indicate that, in IBS patients, both the cognitive-evaluative and affective-motivational dimensions of CNS processing of visceral sensation are diminished for homeostatic regulation of visceral homeostasis, explaining in part the inclination of anxiety in IBS patients in clinical examinations. In addition, reduced hypothalamus connectivity was also identified in clustered areas in the pons in IBS patients in both stimulation conditions, indicating a possible degraded communication in the descending regulatory pathway from the hypothalamus to the brainstem nuclei.

Limitations of the present study and cautions in interpreting the results should be noted. First, as acknowledged in our prior publication [6], the sample size of our study is indeed small, with only eight controls and nine IBS patients. This was mainly due to the difficulty of recruiting adolescent volunteers for an fMRI study, especially with the use of rectal distension involved. We performed two scans in each stimulation condition; this has improved the statistical power. In addition, we showed [6] that the rectal-distension-induced brain activations bear much resemblance to those in the meta-analysis of adult IBS patients [18], partially supporting the quality of our data and analysis. Given the sample size limitation, the findings of this study should be considered preliminary. Second, it is not possible, by the present study itself, to determine whether the observed changes of hypothalamus connectivity are causal or consequential to the disrupted visceral homeostasis in IBS patients. IBS is heterogeneous disorder with a multifactorial pathophysiology including a complex interplay of biological, psychological, and social factors [14].

In summary, we report that hypothalamus functional connectivity in adolescent IBS patients was reduced in neural structures specifically involved in sensory-discriminative, cognitive-evaluative, and affective-motivational aspects of the CNS processing of visceral sensation and pain. Our study supports the disrupted cortical modulation of hypothalamus functioning

is an important contributing factor, in the context of the generalized homeostatic regulation network [1], to the disruption of visceral homeostasis in adolescent IBS patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A–B) Hypothalamus functional connectivity in controls and IBS patients in the subliminal rectal distension condition. (C–D) The same presentation of two groups in the liminal rectal distension condition. (LPFC: lateral prefrontal cortex, STG: superior temporal gyrus, SMA: supplemental motor cortex, AMY: amygdala, HP: hippocampus, PHG: parahippocampal gyrus, dACC: dorsal ACC; pACC: perigenual ACC)

Figure 2.

Two-sample *t*-test comparisons of hypothalamus functional connectivity between the control and IBS patient groups during the subliminal (A) and liminal (B) rectal distension conditions. Significant group differences were shown in both brain surface and sectional anatomical images to highlight cortical and subcortical structures of interest. Warm color indicates greater hypothalamus connectivity in controls.