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Irritable bowel syndrome in female patients is associated with alterations in structural brain networks

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ABSTRACT

Alterations in gray matter (GM) density/volume and cortical thickness (CT) have been demonstrated in small and heterogeneous samples of subjects with differing chronic pain syndromes, including irritable bowel syndrome (IBS). Aggregating across 7 structural neuroimaging studies conducted at *University of California*, *Los Angeles*, *Los Angeles*, *CA*, *USA*, between August 2006 and April 2011, we examined group differences in regional GM volume in 201 predominantly premenopausal female subjects (82 IBS, mean age: 32 ± 10 SD, 119 healthy controls [HCs], 30 ± 10 SD). Applying graph theoretical methods and controlling for total brain volume, global and regional properties of large-scale structural brain networks were compared between the group with IBS and the HC group. Relative to HCs, the IBS group had lower volumes in the bilateral superior frontal gyrus, bilateral insula, bilateral amygdala, bilateral hippocampus, bilateral middle orbital frontal gyrus, left cingulate, left gyrus rectus, brainstem, and left putamen. Higher volume was found in the left postcentral gyrus. Group differences were no longer significant for most regions when controlling for the Early Trauma Inventory global score, with the exception of the right amygdala and the left postcentral gyrus. No group differences were found for measures of global and local network organization. Compared to HCs, in patients with IBS, the right cingulate gyrus and right thalamus were identified as being significantly more critical for information flow. Regions involved in endogenous pain modulation and central sensory amplification were identified as network hubs in IBS. Overall, evidence for central alterations in patients with IBS was found in the form of regional GM volume differences and altered global and regional properties of brain volumetric networks.

1. Introduction

Structural alterations of the brain in the form of higher or lower density of the gray matter (GM) and volume and cortical thickness (CT) have been reported in a wide range of chronic somatic and visceral pain conditions, including chronic inflammatory conditions (osteoarthritis [6,107], chronic pancreatitis [49,127], and Crohn disease [2]); persistent, often comorbid pain syndromes (temporomandibular disorder [51,54,95,115,143]; vulvodynia [115]; chronic pelvic pain [5,97]; irritable bowel syndrome (IBS) [12,35,116]; fibromyalgia [20,75,142]); migraine [71,106,111,140]; chronic tension-type headache [113]; cyclical menstrual pain [137]); and other pain conditions (chronic lower back pain [4,99,112,138] and complex regional pain syndrome [50,53,54,99]). The variability in reported findings may be in part related to the fact that the majority of these studies were relatively small and poorly controlled for medication intake, the presence of comorbid conditions, or sex. The most commonly reported regions related to the lower GM were subregions of cingulate and insular cortices, temporal lobe, prefrontal cortex, and thalamus/basal ganglia [34,88], whereas disease-related regional GM volume increases have been reported in a few studies [94,115,116] involving basal ganglia, hippocampus, anterior cingulate (ACC) subregions, posterior insula,

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and somatosensory cortex (S1). Previously published reports suggest differing patterns of gray matter changes for various types of chronic pain, such as neuropathic and nociceptive pain [53,54].

Recent research examining GM morphometry (volume, surface area, cortical thickness); anatomical connectivity (white matter tractography); and brain function (resting state, task-based) indicate that disease-related symptoms may be associated with altered integration of brain regions that comprise large-scale networks [8,9,17,19,26,57–59,108,110]. In studies examining GM morphometry, anatomical connectivity is inferred from correlated regional GM measures (eg, volumes). Correlation of anatomical features of brain regions across individuals may partly reflect functional interactions among these areas [19,120], mutually trophic effects on growth mediated by axonal connections [45–47], tissue type similarities [19,27], genetics [24,45,114,129], and/or environment-related plasticity [1,45,92,114].

We aggregated data across 7 structural neuroimaging studies conducted at the *University of California*, *Los Angeles*, *Los Angeles*, *CA* (UCLA) between August 2006 and April 2011 and examined group differences in regional GM volume in a large sample of 201 female subjects (82 with IBS, 119 HCs). We applied network analysis to obtain new insights about large-scale regional connectivity and to compare morphological brain architectures and network properties between groups of subjects with IBS and HCs. To assist in our large-scale analyses we employed the Laboratory of Neuro Imaging (LONI) pipeline [39,41,135], a graphical workflow environment that allows users to describe executable tools in a graphical user interface and create processing modules as nodes in a graph representing the complete computational protocol [40,42]. We provide evidence for regional alterations in GM volume as well as differences in the regional properties of large-scale structural brain networks in subjects with IBS compared to HCs.

2. Methods

2.1. Subjects

Female subjects with IBS and HCs were recruited from multiple clinical sites at UCLA, sites that are part of the clinical research network of the Center for Neurobiology of Stress, and from community advertisements. A diagnosis of IBS was made using the Rome Foundation II or III (Raleigh, NC, USA) symptom criteria [86,130] based on assessments by gastroenterologists experienced in the diagnosis of functional bowel disease and the exclusion of organic disease. A gastroenterologist or gastrointestinal (GI) nurse practitioner obtained histories and conducted physical examinations. Patients with IBS who had all types of predominant bowel habits were included. Using clinical histories or questionnaire data, subjects who had histories of any chronic functional symptom or syndrome or symptoms suggestive of disordered mood or affect were excluded. Potential subjects were also excluded if they (1) had serious medical conditions or were taking medications because those factors could interfere with interpretation of the brain imaging or physiological measures; (2) had ongoing major psychiatric diagnoses or were being treated with psychotropic medications that had been used over the past 6 months (subjects were not excluded for lifetime incidence of psychiatric disorders or for intake of low-dose tricyclic antidepressants for nonpsychiatric indications); (3) engaged in excessive physical exercise (eg, marathon runners).

2.2. Structural MRI

Brain images from 201 females (82 with IBS, 119 HCs) were obtained and combined from 7 structural imaging studies conducted at UCLA, using 4 separate protocols. Included in this subject pool were 55 patients with IBS and 48 HCs who had been included in a prior analysis of GM density using voxel-based morphometry [116]. Brain images were acquired on 1.5 or 3T magnetic resonance imaging (MRI) scanners (Siemens Allegra; Olin, Hartford, CT, USA). First, a sagittal scout was used to position the head. Then each subject underwent 1 of 4 structural acquisition sequences using a high-resolution 3-dimensional T1-weighted, sagittal magnetization-prepared rapid gradient echo (MP-RAGE) protocol. See Table 1 and Table 2 for a description of the structural acquisition protocols.

2.3. Phenotype data

We collected phenotyping data on early adverse life events (EALs) (early trauma inventory; ETI) [15]; trait anxiety scores (State Trait Anxiety Inventory; STAI) [121]; depression and anxiety (Hospital Anxiety and Depression Scale; HAD) [144]; catastrophizing (Coping Strategies Questionnaire; CSQ) [105]; and health status (Patient Health Questionnaire; PHQ, using 12 items without GI-related questions) [73]. IBS symptom severity and abdominal pain and duration in the past week were measured on a 21-point numeric rating scale (Bowel Symptoms Questionnaire; BSQ) [98]. Usual symptom severity was assessed on an ordinal scale (1 = none; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe). Menopause status was assessed by self-report.

2.4. Data analyses

2.4.1. Volumetric analysis

The UCLA Laboratory of Neuroimaging (LONI) pipeline was used for image preprocessing and volumetric analysis. Fig. 1 shows the pipeline workflow implementing the volumetric data analysis. The volumetric workflow pipeline consists of 4 main components: (1) data preprocessing (intensity inhomogeneity correction [117]; (2) skull stripping [83,84]; (3) cortical surface modeling [48]; and (4) tissue classification [133,134]. The complete pipeline workflows are available as XML objects that can be downloaded, viewed and tested via the Pipeline environment (pipeline.loni.ucla.edu); see Supplementary Files 1 and 2.

2.4.2. Brain parcellation

Global and regional volumetric analyses rely on dividing the brain into both its differing tissues and 56 predefined brain struc-

Table 1
Details of study MRI acquisition protocols.

	HC (n)	IBS (n)	Age years M (SD) range	Field strength	TR (ms)	TE (ms)	Flip angle (°)	Number of scans
Protocol 1	24	20	29 (11.2) 18–64	3 Tesla	20	3.39	25	44
Protocol 2	26	45	31 (9.3) 19–56	3 Tesla	2300	2.85	9	71
Protocol 3	50	8	32 (9.7) 20–56	1.5 Tesla	1900	4.38	15	58
Protocol 4	19	9	30(10.9) 19–61	1.5, 3 Tesla	2200	3.26	9	28

HC, healthy controls; IBS, irritable bowel syndrome; TE, echo delay time; TR, repetition time; Cohen's d, effect size.