Neuroscience Letters 632 (2016) 141–146

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Distinct resting-state brain activity in patients with functional constipation

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HIGHLIGHTS

- The pathophysiology of functional constipation is still not completely understood.
- We examined the interactions of brain regions underlying functional constipation.
- Stronger effective connectivity from the frontal cortex propelling limbic circuit.
- Weaker connectivity from sensory and motor control regions to limbic circuit.

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 17 August 2016
Accepted 23 August 2016
Available online 25 August 2016

Keywords:
Functional constipation
fMRI
Granger causality
Resting-state
Emotional arousal
Somatic and sensory

ABSTRACT

Functional constipation (FC) is a common functional gastrointestinal disorder (FGID) with a higher prevalence in clinical practice. The primary brain regions involved in emotional arousal regulation, somatic, sensory and motor control processing have been identified with neuroimaging in FGID. It remains unclear how these factors interact to influence the baseline brain activity of patients with FC. In the current study, we combined resting-state fMRI (RS-fMRI) with Granger causality analysis (GCA) to investigate the causal interactions of the brain areas in 14 patients with FC and in 26 healthy controls (HC). Our data showed significant differences in baseline brain activities in a number of major brain regions implicated in emotional process modulation (i.e. dorsal anterior cingulate cortex–dACC, anterior insula–aINS, orbitofrontal cortex–OFC, hippocampus–HIPP), somatic and sensory processing, and motor control (i.e., supplementary motor area–SMA, precentral gyrus–PreCen) ($P < 0.05$, FDR correction). The GCA results revealed stronger effective connectivity from the OFC and dACC, which are regions involved with emotional regulation, propel limbic regions at the aINS and HIPP to induce abnormal emotional processing regulating visceral responses; and weaker effective connectivity from the SMA and PreCen, which are regions involved with somatic, sensory and motor control, propel the aINS and HIPP, suggesting abnormalities of sensory and behavioral responses. Such information of basal level functional abnormalities expands our current understanding of neural mechanisms underlying functional constipation.

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1. Introduction

Functional constipation (FC) is a common functional gastrointestinal disorder (FGID) in clinical practice [2,16,33], with reported prevalence ranging from 0.7 to 29.6% and a mean female to male ratio of 2.1:1 [36]. FC is characterized by infrequent bowel movements, excessive straining, hard and/or large stools, painful defecation, sensation of incomplete evacuation, and is

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http://dx.doi.org/10.1016/j.neulet.2016.08.042
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often accompanied by abdominal pain [2,16]. These symptoms can have a significant impact on the patients' well-being and health-related quality of life [25,33]. Most cases are functional in origin, and they are often related with multiple contributing factors including inadequate nutrition, decreased physical activity, and emotional/behavioral and psychological factors [23]. However, the pathophysiology of FC is still not completely understood.

According to Drossman [8], diagnosing FGID is difficult due to lacking specific causes, hence why it is a functional disorder. Some proposed that FGID is caused by the 2-way brain-gut axis, whose physiological changes to the gastrointestinal system may affect brain functioning and vice-versa, dysregulation of food intake, digestion, gut sensations, and control of bowel movement [29] as well as in FC and irritable bowel syndrome (IBS) [11]. The brain-gut relationship is crucial during stressful periods, affecting behavioral aspects, managing moods and is associated with symptoms of the disease.

Neuroimaging studies showed that FGID was identified with dysfunctional brain areas regulating somatic and visceral pain [3,5] in the primary and secondary somatosensory cortices, thalamus and insular cortex (INS), and the anterior midcingulate cortex (aMCC), anterior insular cortex (aINS) and prefrontal cortex [15,39]. According to Silverman et al. [9], they discovered that painful rectal distension caused greater activation of the left dorsolateral prefrontal cortex (DLPFC) instead of the MCC in FGID compared with healthy controls as in another study [5]. Further research indicated that there was more activation of the emotional arousal network as a result of painful stimuli in various regions including the locus coeruleus complex, amygdala, hypothalamus, hippocampal gyrus (HIPP), perigenual anterior cingulate cortex (pACC), and orbitofrontal cortex (OFC) [18,20].

As far as we know, no functional brain imaging study has been conducted to investigate the neural mechanisms underlying FC. In order to examine the brain functional abnormalities, we first employed resting-state fMRI (RS-fMRI) and an amplitude of low frequency fluctuation (ALFF) analysis [44] to elucidate differences in the basal brain activity between the patients with FC and healthy controls. Next, we performed a Granger causality analysis (GCA) [22,32,41,42], which is an effective connectivity analysis method, to characterize the causal influence between different brain regions that may critically impact functional constipation.

2. Experimental procedure

2.1. Participants

Participants were recruited from a clinical site at Xijing Hospital affiliated with the Fourth Military Medical University in Xi'an, China. Upon arrival at the clinic, each participant read and signed an informed consent form and underwent a full physical exam with history. Diagnosis of FC was made by a gastroenterologist experienced in the diagnosis of FGID using Rome III criteria [8]. The Rome III criteria defines FC as having active symptoms within the last 3 months with symptom onset at least 6 months previously in addition to the presence of at least 2 other symptoms during 25% of the defecations (e.g., stool frequency of <3 per week, straining, feelings of incomplete evacuation, the need for digital manipulation, and rectal pressure or pain) [8]. FC patients with all types of predominant bowel habits (i.e., slow transit constipation, outlet obstruction, and the combination of the two types) were included in this study. The exclusion criteria included psychiatric, neurological, and medical disorders requiring immediate treatment or current medications that could affect the central nervous system. Given the criteria, six subjects were disqualified from the experiment, thus we recruited 14 patients with FC (right-handed, age 44.9 ± 3.8 yrs, range 20–60 yrs, 5 males) and 26 right-handed healthy controls (HC) (age-, education- and gender-matched, $P > 0.05$; age 42.8 ± 3.4 yrs, range 20–60 yrs, 12 males) (Table 1). The experimental protocol was approved by the Institutional Review Board of Xijing Hospital and registered in the Chinese Clinical Trial Registry center under the number: ChiCTR-OOB-15006347 (http://www.chictr.org.cn).

All participants were given a series of self-administered questionnaires to complete, including duration of constipation, sensation of incomplete evacuation, difficulty of defecation, defecation time, abdominal distension and pain (Table 1). They were also asked to complete the ZUNG self-rating depressive scale (SDS), ZUNG self-rating anxiety scale (SAS) and the state-trait anxiety inventory (STAI) to assess their severity of depression and anxiety. STAI was selected for its simplicity, validity and reliability [4,21] and also because it was used to evaluate anxiety levels and to distinguish "state" anxiety from "trait" anxiety in gastrointestinal diseases [13,21].

2.2. MRI acquisition

The experiment was carried out using a 1.5T GE (SIGNA HDXT) scanner. First, a high-resolution structural image for each subject was acquired using three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequences with a voxel size of 1 mm^3 and with an axial fast spoiled gradient echo sequence (TR = 9.1 ms, TE = 3.0 ms, matrix size = 256×256, field of view = 512×512 mm^2 and 248 slices). Then, a gradient echo T2*-weighted echo planar imaging (EPI) sequence was used for acquiring resting-state functional images with the following parameters: TR = 2000 ms, TE = 40 ms, matrix size = 64×64, FOV = 256×256 mm^2, flip angle = 90°, in-plane resolution of 4 mm × 4 mm, slice thickness = 4 mm and 29 axial slices. The scan for RS-fMRI lasted for 400 s (6 min 40 s), containing 200 echo-planar volumes. Subjects were instructed to close their eyes but remain awake and not think about anything during the entire scanning procedure. After scanning, all subjects reported that they had remained awake during the full length of the scan. A radiologist (QL) examined the imaging data and excluded subjects with structural abnormalities.

2.3. Image processing

Imaging data were preprocessed using Statistical Parametric Mapping 5 (SPM5, http://www.fil.ion.uclac.uk/spm), including slice-timing, head movement correction, spatial normalization, band-pass filtering (0.01–0.08 Hz) and global normalization (detailed information see Supplementary information) [42]. The nuisance covariates including head-motion parameters, white-matter signals and cerebrospinal-fluid-signals were regressed out from the BOLD signals.

2.4. ALFF analysis

The amplitude of low frequency fluctuation (ALFF) analysis was carried out using REST software (http://resting-fmri.sourceforge.net) to define the ROIs as that reported in previous studies [42,44] (Supplementary information). Briefly, ALFF is a neuroimaging method that can be used to measure the spontaneous fluctuation in BOLD-fMRI signal intensity, and it has been investigated as a reliable biomarker for many neurological conditions [42,44]. Two sample *t*-tests were employed to compare the differences in ALFF between the FC and control group (FC > HC). The brain regions showing significant ALFF alterations related to brain-gut inter-

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