

Abnormalities of intrinsic brain activity in irritable bowel syndrome (IBS)

A protocol for systematic review and meta analysis of resting-state functional imaging

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Abstract

Background Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders affecting up to 11.5% of the general global population. The brain–gut axis has been shown to play an important role in the pathogenesis of IBS. Several studies confirmed that intrinsic brain abnormalities existed in patients with IBS. But, studies of abnormal regional homogeneity (ReHo) in IBS have reported inconsistent results. The objective of this protocol is to conduct a meta-analysis using the Seed-based *d* mapping software package to identify the most consistent and replicable findings of ReHo in IBS patients.

Method We will search the following three electronic databases: MEDLINE, EMBASE and Web of Science. The primary outcome will include the peak coordinates and effect sizes of differences in ReHo between patients with IBS and healthy controls from each dataset. The secondary outcomes will be the effects of age, illness severity, illness duration, and scanner field strength. The SDM approach was used to conduct voxel-wise meta-analysis. Whole-brain voxel-based jackknife sensitivity analysis was performed to conduct jackknife sensitivity analysis. A random effects model with Q statistics is used to conduct heterogeneity and publication bias between studies and meta-regression analyses were carried out to examine the effects of age, illness severity, illness duration, and scanner field strength.

Results The results of this paper will be submitted to a peer-reviewed journal for publication.

Conclusion This research will determine the consistent pattern of alterations in ReHo in IBS patients.

Abbreviations: IBS = irritable bowel syndrome, RCT = randomized controlled trials, ReHo = regional homogeneity, SMD = standardized mean difference, SRs = systematic reviews.

Keywords: brain–gut axis, fMRI, irritable bowel syndrome, meta-analysis, ReHo

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1. Introduction

Irritable bowel syndrome (IBS) is a widespread functional gastrointestinal disorder characterized by recurrent chronic functional gastrointestinal disorder (FGID) with the typical clinical symptoms of recurrent abdominal pain or discomfort, changes in stool characteristics and bowel habits with a global prevalence of about 11.2% of the population.^[1,2] It is reported that nearly 50% patients with IBS suffer from psychological–psychiatric and approximately 20–40% of patients accompany with depressive symptoms.^[3,4] The interaction of psychosocial factors and gut physiology is the reasons of the pathophysiology of IBS. Studies have shown that anxiety and depression can double the risk of IBS onset.^[5] The brain–gut axis is another powerful reason including central nervous system CNS, neuro–endocrine–immune system, hypothalamic–pituitary–adrenal axis, autonomic nervous system, and enteric nervous system and is a bidirectional system enables to communicate between the central nervous system (CNS) and the gut.^[6] It plays an important role in IBS by regulating gastrointestinal motility, visceral sensitivity, brain gut peptide secretion, stress response, and cognitive function.^[7] But up to now, the neural mechanisms of depressive symptoms in IBS remain unclear. Therefore, further exploration of brain functional changes, such as the intensity of neural activity and functional connectivity (FC) in local brain regions in

patients with IBS between specific brain regions with psychological symptoms (such as depression) will help us understand the pathophysiological mechanisms of brain–gut FGID interaction.

Several results from brain imaging studies suggests that IBS is associated with structural and functional changes in the brain.^[8,9] Seminowicz found that IBS-D was associated with changes of the posterior parietal cortex (PPC)/middle frontal gyrus (MFG)/bilateral ventral striatum/pregenual anterior cingulate cortex (ACC), pain symptoms with MFG, ventral striatum, ventrolateral prefrontal cortex (vlPFC), Orbitofrontal Cortex (OFC), emotional symptom with MFG, hippocampus and thalamus.^[10]

Resting-state fMRI (RS-fMRI) is a more important tool to examine brain functional activities of IBS when intestinal tract is at rest state. Based on the amplitude of low-frequency fluctuation (ALFF) and RS-fMRI, Ma^[11] applied RS-fMRI and the amplitude of low-frequency fluctuation (ALFF) method in IBS patients and found that the left superior frontal gyrus, right MFG, right hippocampus, right superior temporal pole, and bilateral postcentral gyrus exhibited lower ALFF values, while the left calcarine and left median cingulate exhibited higher ALFF values. There was a significant correlation between duration of disease in IBS and ALFF values in the altered regions. Qi^[12] reported that IBS patients had decreased ALFF values in several core default mode network regions and increased ALFF values in the bilateral posterior insula and cuneus.

Regional homogeneity (ReHo) has recently been used as an efficient and reliable neuroimaging marker in the investigation of resting-state regional brain activity in neuropsychiatric disorders such as IBS.^[13] Studies have shown that results of both areas of decreased and increased ReHo are inconsistent.^[13–15] In this context, we considered it was appropriate to conduct a meta-analysis to identify the most consistent and replicable ReHo changes in IBS.

2. Method and design

This protocol is registered in INPLASY (INPLASY202130108). This is an SRs and MA of clinical studies, so ethical approval is not necessary.

2.1. Data sources, study selection, and quality assessment

A comprehensive search of studies published between January 2000 and June 12, 2021 was conducted in the PubMed, Embase, and Web of Science databases using the keywords “Irritable bowel syndrome” OR “Irritable Bowel Syndromes”, OR “Syndrome, Irritable Bowel”, OR “Syndromes, Irritable Bowel”, OR “Colon, Irritable”, OR “Irritable Colon”, OR “Colitis, Mucous”, OR “Mucous Colitides”, OR “Mucous Colitis”, AND “regional homogeneity” OR “ReHo” OR “local connectivity” OR “coherence. Furthermore, the references of the included studies and related review were checked for additional relevant studies. Studies that satisfied the following conditions were included in the meta-analysis:

1. patients had been diagnosed with IBS;
2. ReHo comparison of patients with IBS versus healthy controls was conducted;
3. three-dimensional coordinates (Talairach or Montreal Neurological Institute [MNI]) were reported for the whole-brain ReHo analysis;
4. significant results were reported using thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds;

5. the study was published in a peer-reviewed English language journal. Datasets were excluded if they explicitly indicated patients with IBS diagnosed with comorbid neurological or psychiatric diseases (i.e., cognitive depression or impairment).

For longitudinal studies, only the baseline data were included. For studies reporting both on- and off-state results, only the off-state datasets were included. In cases where patient datasets overlapped between separate articles, only the dataset with the largest sample size and the most comprehensive information was included. The corresponding author of each included study was contacted via email when additional information was required. The quality of each study selected for this meta-analysis was assessed with a 20-point checklist used in a previous meta-analysis of RS-fMRI studies.^[16]

The results of electronic searches will be managed using Endnote X9. Two reviewers (WangC and Li ZM) will review articles identified from different databases according to eligibility criteria independently. Duplicates will be first removed. A third reviewer (Fu B) made the final decision when there is a disagreement between two researchers. The current study was conducted with reference to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analyses of observational studies.^[17]

2.2. Data analysis

2.2.1. Voxel-wise meta-analysis. A meta-analysis of ReHo differences between patients with and healthy controls was conducted using the SDM software package (version 4.31 for Windows) in a standard process (www.sdmproject.com). The SDM approach has been thoroughly described elsewhere.^[18–21] We first extracted peak coordinates and effect sizes (e.g., *t*-values) of differences in ReHo between patients with IBS and healthy controls from each dataset. A standard MNI map of the ReHo differences was then separately recreated for each dataset using an anisotropic Gaussian kernel. The mean map was finally generated by voxel-wise calculation of the random-effects mean of the dataset maps, weighted by the sample size, intra-dataset variability, and between-dataset heterogeneity. To optimally balance false positives and negatives, we used the default SDM kernel size and thresholds (full width at half maximum [FWHM]=20 mm, *P* = .005, uncorrected for FDR, peak height *Z* = 1, cluster extent = 10 voxels). It should be noted that this FWHM kernel is intended to assign indicators of proximity to reported coordinates rather than to smooth any image that is different in nature.^[18,21]

If necessary, a subgroup meta-analysis was further conducted.

2.2.2. Jackknife sensitivity analysis. Following preprocessing of the data, a whole-brain voxel-based jackknife sensitivity analysis was performed to test the robustness of the findings by iteratively repeating the same analysis, excluding one dataset each time.^[19,21]

2.2.3. Analyses of heterogeneity and publication bias. A heterogeneity analysis was conducted using a random effects model with *Q* statistics to explore unexplained between-study variability in the results. Heterogeneous brain regions were obtained using the default SDM kernel size and thresholds (FWHM = 20 mm, *P* = .005, uncorrected for FDR, peak height *Z* = 1, cluster extent = 10 voxels).^[18,21] In addition, Egger’s test was performed using the Stata/SE 12.0 software for Windows (Stata Corp LP, College Station, TX, USA) to assess possible

publication bias by extracting the values from statistically significant relevant peaks between patients with IBS and healthy controls.^[22]

2.2.4. Meta-regression analyses. Meta-regression analyses were carried out to examine the effects of age, illness severity, different disease subtypes (IBS-C OR IBS-D), and scanner field strength, which could potentially influence the analytic results. Statistical significance was determined using a stringent threshold of $P = .0005$ and cluster extent = 10 voxels.^[20,21]

3. Discussion

Resting-state functional magnetic resonance imaging (rs-fMRI) is a novel approach, which can be conducted to examine brain activity independent of stimulation or goal-directed tasks.^[23–25] Regional homogeneity (ReHo), a new indicator of resting-state local brain activity, measures the degree of regional synchronization of fMRI time courses. It calculates the temporal homogeneity of regional brain activity rather than its density, providing information about local coherence or intraregional functional connectivity.^[26] Although the exact biological mechanism of ReHo remains unclear, it is thought to reflect the efficiency of coordinated neuronal activity and can be used to assess local alterations in brain function.^[27,28]

However, findings from these ReHo studies of IBS so far have been inconsistent. In addition, the affected brain regions identified in these studies were diverse with different studies sometimes reporting increased or decreased ReHo in the same brain regions.^[13–15] These reported inconsistencies regarding changes in ReHo in patients with IBS can potentially be ascribed to factors such as sample size, illness severity, IBS subtypes, sex and imaging protocols. We hope that the results of this meta-analysis will help to identify the most consistent and replicable ReHo changes in IBS.

Author contributions

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Funding acquisition: Ye Mao.

Methodology: Ye Mao.

Project administration: FU B.

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Supervision: Han Q, Ye Mao.

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Writing – original draft: Li J.

Writing – review & editing: Ye Mao.

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