

# The prognosis and changes of regional brain gray matter volume in MDD with gastrointestinal symptoms

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**Objective:** It is common that major depressive disorder (MDD) is accompanied by gastrointestinal (GI) symptoms. However, few studies have focused on the clinical characteristics and its possible mechanism, while brain gray matter (GM) structure is important in the pathogenesis of GI symptoms. In this study, we aimed to investigate the basic clinical characteristics and regional GM volume changes in MDD accompanied by GI symptoms.

**Method:** Patients with MDD (n=49) and age, gender, and educational level-matched healthy controls (n=30) were recruited. Patients with MDD were divided into two groups based on the GI status: MDD with (n=27) and without (n=22) GI symptoms. The 24-item Hamilton Depression Rating Scale (HAMD) was administered. T1-weighted anatomical images were obtained and analyzed. Correlation analysis was used to identify the possible associations between changed regional GM volume and GI symptoms and depressive symptoms.

**Results:** The HAMD reductive ratio for 2 weeks of treatment in the GI symptoms group was significantly higher than the non-GI symptoms group ( $P < 0.05$ ). The regional GM volume showed significant differences among the three groups (Gaussian Random Field [GRF] correction, voxel- $P < 0.01$ , cluster- $P < 0.05$ ). Compared with non-GI symptoms group, GI symptoms group exhibited significantly increased GM volume in the left hippocampus, left parahippocampal gyrus, right parahippocampal gyrus; and decreased GM volume in the right middle frontal gyrus, right precentral gyrus, right cuneus, right precuneus, right superior occipital gyrus (GRF correction, voxel- $P < 0.01$ , cluster- $P < 0.05$ ). These altered brain areas were correlated with the GI symptoms, not depressive symptoms.

**Conclusion:** The changed regional brain GM volume in GI-MDD group may be the pathogenesis for the GI symptoms. In addition, the GI symptoms may predict the prognosis of MDD.

**Keywords:** major depressive disorder, gastrointestinal symptoms, clinical characters, gray matter volume

## Introduction

Major depressive disorder (MDD) is a complex mental disorder caused by many factors. It is estimated currently that the population living with depression is 322 million worldwide and accounts for approximately 4.4% of the world's population according to the WHO.<sup>1</sup>

In addition to the psychiatric symptoms, somatic symptoms are often reported in patients with MDD. Majority of MDD have somatic symptoms such as headache, anorexia, constipation, back pain, lack of energy, sleep disturbance and so on. It is

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reported that more than 69% of the depressed patients experienced somatic symptoms.<sup>2</sup> It is also shown that patients with mental disorder have an average of six somatic symptoms over the past month.<sup>3,4</sup> Somatic symptoms are common among inpatients and outpatients across all cultures.<sup>5</sup> Moreover, it is reported that the somatic symptoms including gastrointestinal (GI) symptoms are associated with increased severity of depressive symptoms, cognitive impairments and poor prognosis of MDD.<sup>6</sup>

Indeed, the main reasons for patients with depression to seek medical advice are the somatic symptoms.<sup>7</sup> These findings suggest that somatic symptoms are the important parts of depressive episodes. According to nationwide epidemiologic study, García-Campayo et al found that the somatic symptoms are strongly associated with the severity of depression, quality of life (QOL), as well as health resources utilization.<sup>8</sup> Among these somatic symptoms, GI symptom is the most frequent symptom in MDD. In clinic, there are about 67–71% of patients with depression suffering from anorexia and constipation, the incidence of other GI symptoms is 36–63%.<sup>9</sup> For patients with depression, the GI symptoms are so prominent and persistent that they can be diagnosed as functional gastrointestinal disorders (FGIDs).<sup>10</sup> The GI symptoms in patients with MDD influence patients' health care seeking, depression severity and prognosis. They often visit the digestive department for the GI symptoms including abdominal pains, abdominal distension, heartburn, acid regurgitation, nausea and vomiting, eructation, borborygmus, increased flatus and so on. Mussell et al found the incidence of anxiety and depression increased with severity and frequency of GI symptoms in a stepwise manner. In primary care clinics, the prevalence of MDD and anxiety in patients with GI symptoms was more than four times compared to these without GI symptoms.<sup>11</sup> Bekhuis et al reported that the GI symptoms significantly predicted the two-year persistence of MDD.<sup>12</sup> Meanwhile, among the patients with digestive system disease such as FGIDs, the rates of anxiety and depression were 61.5% and 57.0%, respectively, which is significantly higher than the general population (5%).<sup>13</sup>

In conclusion, GI symptoms are closely related to depression and anxiety. However, the pathophysiology of mood-related GI symptoms still remains incompletely understood. In addition to peripheral abnormalities, such as hypersensitivity, GI dysmotility and the dysfunction of the brain–gut axis (BGA), might play a crucial role in the onset and development of the disease. It is increasingly recognized that the two-way communication of BGA have an important effect on the

function of the gut and brain.<sup>14</sup> Accumulating evidence suggests that the depressive symptoms and GI symptoms of patients with depression may have common pathophysiological mechanisms which may involve the alteration of gut microbiota, immune dysfunction, neuro-endocrine disorders, metabolic disturbance and changes of brain structure as well as function. These disorders are involved in the Bi-directionality of brain–gut Interactions.<sup>15–18</sup> So internal and external stimulations can cause emotional changes by BGA. At the same time, the function of GI and other peripheral organs will also be altered.

As early as the 1990s, professor Mearin proposed that the abnormalities of BGA are one of the disease-driven factors behind FGID.<sup>19</sup> By using brain imaging techniques, there are increasing evidence supporting that abnormal processing of sensory information at the central nervous system (CNS) is one of the pathophysiologicals of FGID and various brain networks, including sensory and salience networks might be relevant.<sup>20,21</sup> Positron emission tomography (PET) and fMRI have verified subjects with FGIDs showed altered brain activity during resting-state and GI distension. However, studies exploring brain structure changes in depressive patients with GI symptoms using fMRI were rare.<sup>22</sup>

In this study, we aimed to investigate the prognosis of MDD with GI symptoms and the regional gray matter (GM) volume changes, furthermore, to explore the possible correlation of changed regional brain GM volume and the GI symptoms.

## Methods

### Participants

Forty-nine first-episode, drug-naive patients with MDD were recruited from the Department of Psychiatry in the First Hospital of Shanxi Medical University between December 2016 and July 2017. The MDD diagnosis was made using the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-5).<sup>23</sup> They were interviewed the Chinese version of the Modified Structured Clinical Interview for DSM-5 patient version<sup>24</sup> and interviewed using the 24-item HAM-D.<sup>25</sup>

All the subjects included in this study meet the following criteria: 1) aged from 18 to 55 years old; 2) right-handedness; 3) without history of neurological illnesses or other severe diseases; 4) without history of head injury or other comorbid DSM-IV axis I psychiatric disorders; 5) without GI disease; 6) not pregnant or contraindications for MRI scans.

The eligible MDD patients were divided into two groups by the 12th item (GI symptoms) of the HAMD; GI symptoms include abdominal pains, abdominal distension, heartburn, acid regurgitation, nausea and vomiting, eructation, borborygmus, increased flatus, decreased passage of stools, increased passage of stools, loose stools, hard stools, urgent need for defecation, feeling of incomplete evacuation and so on. This item scores from 0 to 2. Zero means no GI symptoms, 1 means occasional discomfort and the GI symptoms is mild, 2 means frequent discomfort with severe symptoms. Among all the participants, 27 patients had at least one of GI symptoms (GI symptoms group) with the item score is 1 or 2 and 22 patients without GI symptoms (non-GI symptoms group), the item score is 0. Three subjects in GI symptoms group and one subject in non-GI symptoms group were excluded due to excessive head motion during fMRI scan. So there were 24 subjects in the GI symptoms group and 21 subjects in the non-GI symptoms group. After receiving antidepressant treatment (all the participants were taking selective serotonin reuptake inhibitors, ie, fluoxetine (20–40 mg/d) for two weeks, all patients were interviewed using HAMD-24 again.

In addition, 30 right-handed healthy controls (HCs group) whose age, gender and years of education matched were recruited from the Physical Examination Center of the First Hospital of Shanxi Medical University. Subjects with mental disorders, neurological illness, GI disease and abnormalities on brain images were excluded. There was no statistical difference among the three groups in terms of age, gender and years of education. The HAMD scores between GI symptoms group and Non-GI symptoms group were not statistically different.

After receiving a thorough description of the study, all participants provided their written informed consent; this study was approved by the Ethical Committee for Medicine of First Hospital of Shanxi Medical University, Taiyuan, China, and conducted in accordance with the Declaration of Helsinki.

## Image acquisition

We obtained a series of MRI images using a Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany). To reduce head motion and scanner noise, foam pads and earplugs were used during scanning. A 3D-FLASH sequence was used to obtain high-resolution transaxial T1-weighted anatomical images for Voxel-Based Morphometry (VBM) with the following parameters: 120 sagittal slices, TR=14 ms, TE=4.92

ms, thickness/skip=1.5/0.3 mm, FOV=230×230 mm, matrix=256×192 mm, flip angle=25°. The participants were asked to remain awake, close their eyes and relaxed during scanning.

## Image processing

SPM 8 and the VBM 8 toolbox were used for T1 image processing. T1 images are normalized to a template space and segmented into GM, white matter and cerebrospinal fluid. After the preprocessing step, a quality check was taken using the modules “Display one slice for all images” and “Check sample homogeneity using covariance”. Normalized images need to be smoothed with an 8-mm full-width at half-maximum Gaussian kernel.

## Statistical analyses

IBM SPSS Statistics Version 23.0 was used to determine whether there were differences in demographic and clinical characters in the GI symptoms group, non-GI symptoms group and HCs group. Chi-squared test was used to compare gender across groups. Independent two-sample *t*-test was done for the analysis of the seven factors and total score of HAMD and also for the HAMD reductive ratio of 2 weeks. One-way ANOVA was used to compare age and years of education for the three groups.

Voxel-based comparison of VBM maps in the three groups was performed using a design model of full factorial in SPM8. On the basis of the results, two-sample *t*-test was used for comparison between two groups; REST 2.1 ([www.restfmri.net](http://www.restfmri.net)) was used to report the results. The brain areas were considered significant by the GRF correction, voxel-*P*<0.01, cluster-*P*<0.05, the extent threshold was set to 50 voxels.

The differentiated brain areas of GM of all the subjects were extracted using REST.

Correlation analyses (Spearman correlation and Pearson correlation) were conducted to calculate the correlation coefficient between the GM volume of regions of interest and GI symptoms and the total score of HAMD in the MDD groups.

## Results

### The reductive ratio in two groups

The HAMD reductive ratio of the GI symptoms group is significantly lower than the non-GI symptoms group (Table 1). Further, the reductive ratio ( $r = -0.346$ ,  $P = 0.022$ ) was negatively correlated with the GI symptoms (Table 4).

**Table 1** Demographic and clinical characteristics of all participants

Variable	GI symptoms group (n=24)	Non-GI symptoms group (n=21)	HCs group (n=30)	$\chi^2/t/F$ -value	P-value
Gender (M/F)	9/15	10/11	16/14	1.35	0.508 <sup>a</sup>
Age (years)	34.79±10.71	34.14±10.24	33.43±8.98	0.13	0.882 <sup>b</sup>
Education (years)	12.75±2.88	13.29±3.04	13.97±3.10	1.10	0.337 <sup>b</sup>
HAMD					
Total scores	25.50±2.55	24.48±2.77	—	1.29	0.204 <sup>c</sup>
HAMD reductive ratio for 2 weeks anti-depression	0.24±0.14	0.34±0.16	—	2.28	0.028 <sup>c*</sup>

**Notes:** <sup>a</sup>P-value for chi-square test. <sup>b</sup>P-values for one-way ANOVA. <sup>c</sup>P-values for two-sample t-test. \* significant difference.

**Abbreviations:** HAMD, Hamilton Depression Rating Scale; HC, healthy control; GI: gastrointestinal symptom.

## Regional GM volume differences in GI symptoms group, non-GI symptoms group and HCs group

According to full factorial model analysis, we found that the regional GM volume in the left hippocampus, left parahippocampal gyrus, right parahippocampal gyrus, right middle frontal gyrus, right precentral gyrus, right cuneus, right precuneus and right superior occipital gyrus showed significant differences among the three groups (see Table 2 and Figure 1).

## Regional GM volume differences between two groups

Compared with non-GI symptoms group, GI symptoms group exhibited significantly increased GM volume in the left hippocampus, parahippocampal gyrus, right parahippocampal gyrus and decreased GM volume in the right middle frontal gyrus, precentral gyrus, rcuneus, precuneus and superior occipital gyrus (see Table 3 and Figure 2).

Compared with HCs group, increased GM volume was observed in the non-GI symptoms group in the right cuneus, precuneus, superior occipital gyrus, reduced GM volume in the left hippocampus, parahippocampal gyrus and right parahippocampal gyrus (see Table 3 and Figure 3).

The GI symptoms group showed decreased GM volume in the left parahippocampal gyrus, right precuneus and the middle frontal gyrus (see Table 3 and Figure 4).

## Associations between the regional GM volume and clinical data

As shown in Table 3, the GM volume in the left hippocampus and parahippocampal ( $r=0.422$ ,  $P=0.004$ ) and right parahippocampal ( $r=0.359$ ,  $P=0.016$ ) were positively correlated with the GI symptoms. GM volume in the right precentral and middle frontal gyri ( $r=-0.614$ ,  $P<0.001$ ), right cuneus, right precuneus and right superior occipital gyrus ( $r=-0.412$ ,  $P=0.005$ ) were inversely correlated with GI symptoms. Pearson's correlation was performed between the regional GM volume with significant differences and HAMD-24 total scores. However, this relationship was not observed ( $r=0.181$ ,  $P>0.05$ ) (see Table 4).

## Discussion

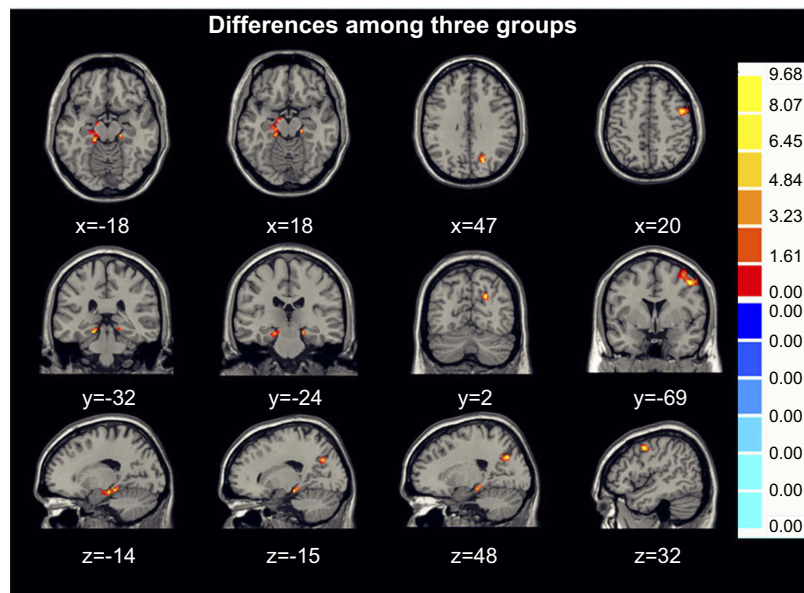
This is, to the best of our knowledge, the first study to compare regional brain structure between MDD with

**Table 2** Regional GM volume differences in GI symptoms group, non-GI symptoms group and HCs group

Brain areas	Cluster size	BA	L/R	MNI coordinates <sup>a</sup>			F-value <sup>b</sup> (peak)
				x	y	z	
Parahippocampal gyrus and hippocampus	279	30,35	L	-18	-32	-14	8.702
Parahippocampal gyrus	58	30	R	18	-24	-15	8.734
Middle frontal and precentral gyri	464	6	R	47	2	48	9.681
Superior occipital gyrus, Cuneus and Precuneus	170	18,7,23	R	20	-69	32	9.193

**Notes:** <sup>a</sup>Coordinates of primary peak locations in the Montreal Neurological Institute space. <sup>b</sup>F-statistical value of peak voxel showing GM volume differences among three groups. Adjusted by GRF (voxel- $P<0.01$ , cluster- $P<0.05$ , cluster size $>50$ ).

**Abbreviations:** BA, Brodmann area; MNI, Montreal Neurological Institute; HC, healthy control; GI: gastrointestinal symptom; GM, gray matter; GRF, Gaussian Random Field.



**Figure 1** Regional GM volume differences in GI symptoms group, non-GI symptoms group and HCs group are displayed on axial, coronal and sagittal slices. Numbers indicate x, y and z slices and are displayed in MNI coordinates. Red color denotes increased GM volume. The color bars indicate the F-value based on one-way ANOVA in three groups. (voxel- $P < 0.01$ , cluster- $P < 0.05$ , cluster size  $> 50$ , GRF correction).

**Abbreviations:** GM, gray matter; HC, healthy control; GI: gastrointestinal symptom; GRF, Gaussian Random Field.

**Table 3** Regional GM volume differences between two groups

Brain areas	Cluster size	BA	L/R	MNI coordinates			T-value (peak)
				x	y	z	
<b>GI symptoms &gt; non-GI symptoms</b>							
parahippocampal gyrus and hippocampus	163	30,35	L	-21	-21	-17	2.920
paraHippocampal gyrus	50	30	R	18	-24	-14	2.817
<b>GI symptoms &lt; non-GI symptoms</b>							
Superior occipital gyrus, Cuneus and Precuneus	165	18,7,23	R	20	-70	30	-2.954
Middle frontal and precentral gyri	464	6	R	47	3	50	-4.818
<b>Non-GI symptoms &gt; HC</b>							
Superior occipital gyrus, cuneus and precuneus gyri	170	18,19	R	20	-69	33	4.023
<b>Non-GI symptoms &lt; HC</b>							
Parahippocampal gyrus and hippocampus	279	30,35	L	-17	-32	-12	-4.246
Parahippocampal gyrus	58	30	R	18	-24	-15	-4.105
<b>GI symptoms &gt; HC</b>	—						
<b>GI symptoms &lt; HC</b>							
Parahippocampal gyrus	53	30	L	-18	-36	-12	-3.040
Middle frontal gyrus	184	6	R	35	5	51	-2.608

**Notes:** MNI coordinates: Coordinates of primary peak locations in the Montreal Neurological Institute space. T-statistical value of peak voxel showing GM volume differences among two groups. Adjusted by GRF (voxel- $p < 0.01$ , cluster- $p < 0.05$ , cluster size  $> 50$ ).

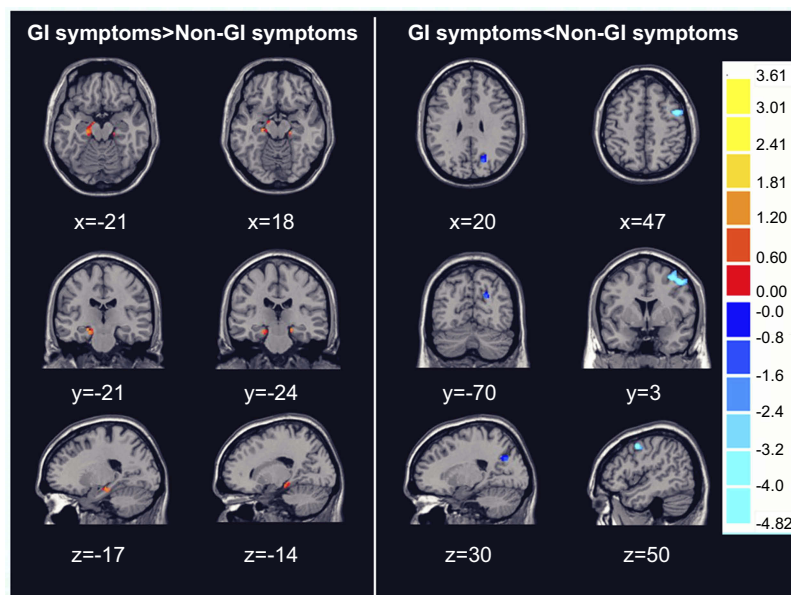
**Abbreviations:** BA, Brodmann area; MNI, Montreal Neurological Institute; GM, gray matter; HC, healthy control; GI: gastrointestinal symptom; GRF, Gaussian Random Field.

and without GI symptoms. This study reveals the basic clinical characters of MDD with GI symptoms and shows the differences in regional brain GM volume between the MDD with and without GI symptoms. Furthermore, this study preliminarily explored the correlations between abnormal brain GM volume and GI symptoms.

## The basic clinical characters of MDD with GI symptoms

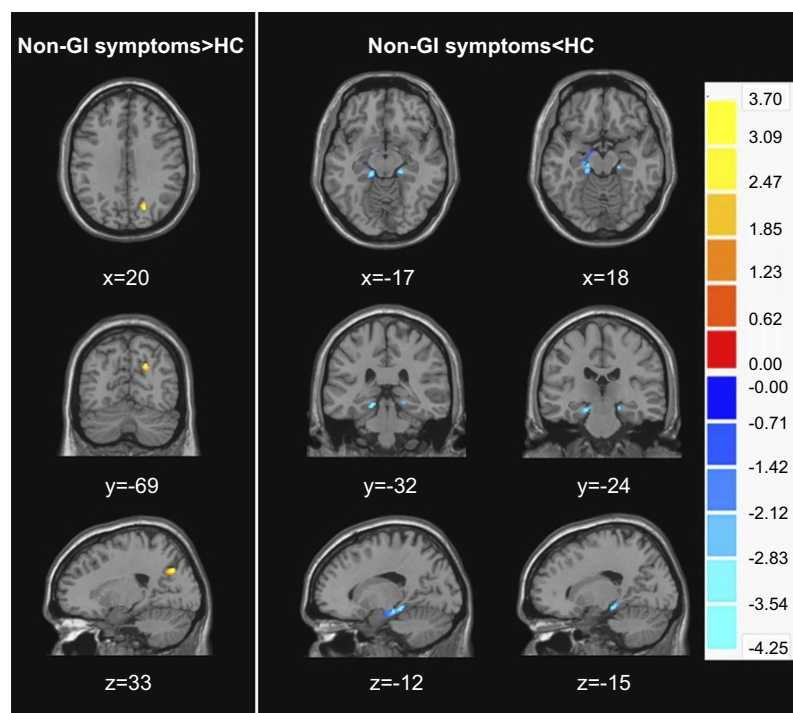
This is, to the best of our knowledge, the first study to compare regional brain structure between MDD with and without GI symptoms. This study reveals the basic clinical characters of MDD with GI symptoms and shows the





**Figure 2** Regional GM volume differences between GI symptoms group and non-GI symptoms group displayed on axial, coronal and sagittal slices. Numbers indicate x, y and z slices and are displayed in MNI coordinates. Red and blue colors denote increased and decreased GM volume. The color bars indicate the T-value based on two-sample t-test. (voxel-  $P < 0.01$ , cluster-  $P < 0.05$ , cluster size  $> 50$ , GRF correction).

**Abbreviations:** GM, gray matter; MNI, Montreal Neurological Institute; GI: gastrointestinal symptom; GRF, Gaussian Random Field.

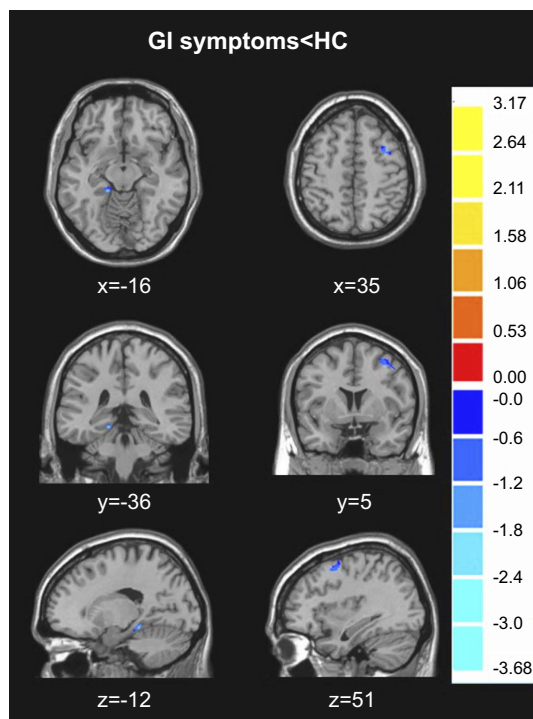


**Figure 3** Regional GM volume differences between non-GI symptoms group and HCs group displayed on axial, coronal and sagittal slices. Numbers indicate x, y and z slices and are displayed in MNI coordinates. Red and blue colors denote increased and decreased GM volume. The color bars indicate the T-value based on two-sample t-test. (voxel-  $P < 0.01$ , cluster-  $P < 0.05$ , cluster size  $> 50$ , GRF correction).

**Abbreviations:** HC, healthy control; GM, gray matter; MNI, Montreal Neurological Institute; GI: gastrointestinal symptom; GRF, Gaussian Random Field.

differences in regional brain GM volume between the MDD with and without GI symptoms. Furthermore, this study preliminarily explored the correlations between abnormal brain GM volume and GI symptoms.

In this study, we found that the total scores of HAMD were not significant between GI symptoms group and non-GI symptoms group. Further, compared with non-GI symptoms group, we found that the score of HAMD



**Figure 4** Regional GM volume differences between GI symptoms group and HCs group displayed on axial, coronal and sagittal slices. Numbers indicate x, y and z slices and are displayed in MNI coordinates. Blue color denotes decreased GM volume. The color bars indicate the T-value based on two-sample t-test. (voxel-  $P < 0.01$ , cluster-  $P < 0.05$ , cluster size  $> 50$ , GRF correction).

**Abbreviations:** HC, healthy control; GM, gray matter; MNI, Montreal Neurological Institute; GI: gastrointestinal symptom; GRF, Gaussian Random Field.

reductive ratio is lower in GI symptoms group after antidepressant treatment for 2 weeks. This indicates that the depression without GI symptoms has a better prognosis.

Previous studies found that somatic symptoms including GI symptoms are strongly associated with the severity of depression.<sup>26</sup> However, our result showed that there is no correlation between the GI symptoms and severity of depression ( $R=0.18$   $P>0.05$ ), which may be related to the small sample size (45 patients) and disease type (MDD patients in our study).

Generally, the 2 weeks reduced ratio of HAMD-24 of anti-depression treatment can predict the response and prognosis of depression to the drug. Silverstein et al found that depressions accompanied by somatic symptoms have a poor response to antidepressant medication in comparison with depressions without somatic symptoms.<sup>27</sup> Xie et al concluded that depressive symptoms improved more slowly and the therapeutic effect is poorer in patients with GI symptoms than those without GI symptoms.<sup>28</sup> In this study, we found that the efficacy is better in depression without GI symptoms after antidepressant treatment for 2 weeks. So we speculate that the non-GI symptoms group may have a better prognosis. It was necessary to take individualized therapeutic schedules for depressions with GI symptoms in clinical. Firstly, patients with GI symptoms significantly heavier than emotional cognitive symptoms may have an insufficient motivation or even resistance to antidepressant treatment. So, psychiatrists should communicate with patients and their relatives deeply to make patients realize that GI symptoms are only symptoms of depression, and the GI symptom is one of the major prognostic factors. Secondly, the depressed patients with severe GI symptoms are difficult to recover after 6–8 weeks of regular antidepressant therapy, so the dose required for treatment is higher, or even need to combine with synergist (such as lithium) and drugs improving GI symptoms.<sup>29–31</sup>

## Differences in regional brain GM volume between non-GI symptoms group and HCs group

The VBM is of great significance for understanding the pathogenesis of the disease. The comprehensive analysis of brain GM volume can determine abnormal brain structure in patients and may find structural neuroimaging biomarkers for diagnoses.

Compared with HCs group, non-GI symptoms group showed increased GM volume in the right cuneus, right

**Table 4** The correlation between the regional GM volume and clinical characteristics

Variable		The total scores of HAMD coefficient P-value		GI symptoms coefficient P-value	
Brain areas	Parahippocampal gyrus and hippocampus	0.258	0.087 <sup>d</sup>	0.422	0.004 <sup>e*</sup>
	Parahippocampal gyrus	−0.233	0.141 <sup>d</sup>	0.359	0.016 <sup>e*</sup>
	Superior occipital gyrus, Cuneus and Precuneus	−0.092	0.548 <sup>d</sup>	−0.614	0.001 <sup>e*</sup>
	Middle frontal and precentral gyri	−0.195	0.200 <sup>d</sup>	−0.417	0.004 <sup>e*</sup>
Clinical characteristics	HAMD reductive ratio for 2 weeks	—		−0.340	0.022 <sup>e*</sup>

**Notes:** <sup>d</sup> P-value for Pearson correlation. <sup>e</sup> P-values for Spearman correlation. \* Statistical significance.

**Abbreviations:** HAMD, Hamilton Depression Rating Scale; GM, gray matter; GI, gastrointestinal symptom.

precuneus and right superior occipital gyrus and reduced GM volume in the left hippocampus, left parahippocampal gyrus and right parahippocampal gyrus. Our results are the same as previous reports. For example, a voxel-based meta-analysis which included 41 studies including 50 comparisons between MDD (1736 patients) and healthy controls (2365 controls) showed that regions of greater volume relative to healthy controls were observed in the right postcentral gyrus, bilateral superior occipital gyrus and right cuneus. Smaller volumes were found in the right middle frontal gyrus, left hippocampus and left parahippocampal gyrus.<sup>32</sup> Another meta-analysis found that MDD patients presented increased GM volume in the bilateral cuneus and left paracentral gyrus, compared to healthy controls and reduced volume in the bilateral hippocampus.<sup>33</sup> Compared with controls, Wise et al found GM volume reductions in bilateral hippocampal and parahippocampal gyrus in MDD patients by meta-analyses. Furthermore, patients with MDD who were currently depressed had a significantly smaller hippocampal volume compared with patients in remission.<sup>34</sup> However, the results of these studies are not completely consistent. The GM volume in hippocampus was decreased in all studies. The possible reasons for the inconsistent results were that different studies had distinct demographic characteristics, various imaging acquisition techniques and diverse methods to analyze data.

The hippocampus may influence memory of emotional information, and the signal communication with other regions plays an important role in mood regulation. The hippocampus has been implicated in many mood disorders, with its volume deficits. Indeed, studies in adults have reported reduced hippocampal subfield volumes in both patients with MDD and bipolar disorder. Hippocampus volume reduction has a significant impact on the brain's executive function, stress regulation and learning process.<sup>35,36</sup> In this study, we also found the GM volume changes in cuneus, precuneus and occipital cortex in MDD. The occipital cortex is responsible for the collection and processing of visual information. Alterations of occipital cortex structure may affect the neuropsychological activity of attention and memory which are closely related to visual function. The precuneus located in the medial parietal lobe is thought to be associated with high levels of cognitive function.<sup>37</sup> Precuneus is part of the Default Mode Network (DMN). Previous rs-fMRI studies showed that the DMN change plays an important role in pathogenesis of MDD patients.<sup>38</sup>

## Differences in regional brain GM volume between GI symptoms group and non-GI symptoms group

The most important finding of this study was that GI symptoms group exhibited significantly increased GM volume in the left hippocampus, left parahippocampal gyrus and right parahippocampal gyrus and decreased GM volume in the right middle frontal gyrus, right precentral gyrus, right cuneus, right precuneus and right superior occipital gyrus. Furthermore, a correlation analysis was performed. We found that GM volume of identified brain regions correlated with GI symptoms.

There had been a lot of neuroimaging studies on FGID. Brain dysfunctions in FGID have been identified. Zeng et al showed that compared with healthy subjects, patients with FD had higher levels of glycometabolism in prefrontal cortex (PFC), precentral gyrus, postcentral gyrus, right parahippocampal gyrus and left precuneus cortex.<sup>39</sup> Van Oudenhove et al used PET techniques and found that occipital cortex, precuneus cortex, hippocampus-amygdala, PFC, and anterior cingulate cortex extensively deactivated during gastric distension in health.<sup>40</sup> Seminowicz et al found that patients with IBS exhibited decreased gray matter density (GMD) in medial prefrontal cortex, ventrolateral prefrontal cortex and posterior parietal cortex and increased GMD in (para)hippocampus, and left dorsolateral prefrontal cortex.<sup>41</sup> It has been suggested that the GM volume in patients with chronic pain syndromes shows extensive changes.<sup>42</sup> Although the results of these studies are inconsistent, they all pointed out that the dysfunction of CNS may be one of the important pathophysiological mechanisms causing GI symptoms. Our findings were not entirely consistent with previous studies. The possible reasons were that our samples were different from previous studies in size, demographic characteristics and disease type. Further, we used different imaging acquisition techniques and different data analysis method.

The PFC of the brain located on the top hierarchy of visceral sensory network is related to executive and integrative control functions. The cognitive modulation of pain, integration of peripheral information, and response or appraise to affective aspect of pain sensation are performed in the PFC.<sup>43</sup> Hippocampus and parahippocampal are important brain regions that are located in the limbic system. In CNS, the functional nucleus associated with the regulation of GI function mainly is located in the limbic system which plays an important role in controlling human emotions,



visceral pain and visceral sensation. So the limbic system is also thought as the core of uniting mind and body.<sup>20</sup> Precuneus is part of the DMN which is closely related to cognitive and executive functions, such as visual processing, auditory processing, memory, motivation, emotional processing and self-instruction. Many studies showed the importance of the DMN in the pathophysiology of somatization disorder including GI dysfunction.<sup>23</sup> To a certain extent, the abnormal persistent activity in the DMN was related to GI symptom severity.<sup>44</sup> Although the occipital cortex was frequently reported in functional neuroimaging studies in FGID patients,<sup>45</sup> the exact mechanism is still unclear. Previous studies showed that nausea was correlated with the activity of occipital gyrus and that a gastric electrical stimulation can increase the occipital cortex activity.<sup>46</sup> These brain regions are associated with the information processing of visceral sensory and visceral motor, so GM volume changes in these brain regions may be related to the GI symptoms.

In this study, we also found that the abnormal brain regions in patients with MDD (comparing non-GI symptoms group with HCs group) and that in the patient with GI symptoms (comparing GI symptoms group with non-GI symptoms group) were nearly consistent. These same brain regions were the left hippocampus, parahippocampal gyrus, right parahippocampal gyrus, cuneus, precuneus and the superior occipital gyrus. This further explains the comorbid-ity pathophysiological mechanism of MDD and GI diseases.

## Limitations

There are several limitations in our study. Firstly, we divide groups by the 12th item (GI symptoms) of the HAMD. It might be better to assess the gastrointestinal symptom rating scale so that it is clear which GI symptom MDD patients have and the severity of GI symptom. Secondly, this is a cross-sectional study, whether GM volume changes are a preexisting abnormality or a consequence of GI symptoms are needed to be examined, long-term follow-up observations and GM volume changes between pretreatment and posttreatment can lead to more profound experimental results. Lastly, there is a relatively small sample size.

## Conclusion

In summary, the present study showed the different clinical characters and regional brain GM volume between the GI symptoms group and non-GI symptoms group. Furthermore, we found that the anxiety/somatization, cognitive impairment, weight loss factors and changes of regional brain

GM volume in depressed patients are associated with GI symptoms. The accompanied GI symptoms are associated with the prognosis of depression. The current results might provide evidence to support the mechanism of GI symptoms in depression and are helpful for clinical therapy.

## Ethics approval and consent to participate

The Ethical Committee for Medicine of the First Hospital of Shanxi Medical University approved this study. Written informed consent was received from all participants prior to inclusion.

## Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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