



Evaluation of neostriatum changes in Crohn's disease: a multimodal brain magnetic resonance imaging study

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Background: Abnormalities of neostriatum have been reported to be implicated in Crohn's disease (CD). However, there are few systematic explorations. We aim to explore the changes that occur in the structure and function of the neostriatum and whether these changes are related to the clinical characteristics of CD.

Methods: In this cross-sectional and prospective study, we enrolled 34 CD patients and 31 healthy controls (HCs) for analysis. We performed voxel-based morphometry (VBM) and seed-based functional connectivity (FC) to evaluate the structural and functional changes in the neostriatum. Correlation analysis was used to evaluate the possible relationships between clinical characteristics and neuroimaging findings.

Results: CD patients had significantly increased gray matter volume (GMV) in the bilateral putamen compared with HCs. The results showed that CD patients had significantly decreased FC related to the putamen-calcarine cortex, putamen-fusiform gyrus, putamen-inferior temporal cortex (ITC), putamen-parahippocampus, and increased FC associated with the putamen-cuneus/precuneus. Moreover, CD patients showed a positive correlation between the GMV in the left putamen and illness duration ($r=0.42$, $P=0.013$).

Conclusions: Our study indicated that CD patients had increased GMV and abnormal FC related to the putamen. The structural and functional differences could reflect that neostriatum may be linked with alterations of aberrant patterns of the default mode network (DMN) and visual processing area.

Keywords: Crohn's disease (CD); neostriatum; voxel-based morphometry (VBM); functional connectivity (FC); magnetic resonance imaging (MRI)

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Introduction

Several lines of evidence have demonstrated that the neostriatum is composed of the caudate nucleus and putamen (1-4). As the primary input part of the basal ganglia, the neostriatum receives information from the cerebral cortex and thalamus. The neostriatum can be roughly divided into sensorimotor regions processing sensorimotor information, social regions processing cognitive information, and regions for reward and motivation information (5,6). Specifically, its subregions are enrolled in goal-oriented (action result) and habitual (stimulus response) learning (7). Previous studies have shown that the neostriatum is associated with certain disorders, such as Parkinson's disease, drug addiction, Huntington's disease, depression, and schizophrenia (8,9). On the base of brain-gut axis theory, the neostriatum has also been found to be involved in gastrointestinal diseases including inflammatory bowel diseases (IBDs) as well as irritable bowel syndrome (IBS) (10,11).

As one IBD subtype, Crohn's disease (CD) is characterized by repeated attacks of intestinal inflammation, abdominal pain, chronic diarrhea, weight loss, etc. (12-14). CD causes widespread high-level stress, anxiety and a decline in sleep quality (15,16). Worldwide prevalence of CD in adults and children is increasing year by year (14,17). The etiology of CD is complex and is currently considered to be implicated in the interaction of genetic factors, environmental factors and changes in intestinal flora (12,17). However, the inflammatory response of the gastrointestinal tract can not sufficiently explain processes related to psychological stress and anxiety, as well as depression (18). In fact, the pathophysiology of CD has transcended the gastrointestinal tract. There is a two-way exchange of information between various visceral signals from the gastrointestinal tract and nerve signals in the brain (19). This mechanism may suggest that neural abnormalities in brain regions are associated with brain-gut axis disorders (18,20).

Recent neuroimaging studies have indicated the complex two-way interaction between brain and gut in CD, specially related to neostriatum (21-23). Bao *et al.* found significantly changed gray matter volume (GMV) of the putamen, globus pallidus, insula and other regions in CD patients compared to healthy controls (HCs), and the left insula and orbitofrontal cortex were negatively correlated with disease duration (24). Li *et al.* found that the putamen in CD patients had higher regional homogeneity (ReHo) values compared to those of the HCs (21). Zhang *et al.* found altered functional connectivity (FC) of insula with the caudate

nucleus, parahippocampus/hippocampus and other brain areas in CD patients, and the FC of the parahippocampus/hippocampus with insula were negatively correlated with Crohn's Disease Activity Index (CDAI) (22). Goodyear *et al.* observed significantly increased activity and FC in cognitive and emotional processing brain regions, including parts of the limbic system, basal ganglia, and hypothalamus of IBD patients compared to HCs, especially the volume of the thalamus was positively correlated with C-reactive protein (CRP) concentration and was increased in females experiencing pain (23). It was also found that the amygdala, putamen and other brain regions of CD patients were implicated in pro-inflammatory reactions and autonomic stress reactions, and regulated changes in stress habits (25). Although abnormalities of neostriatum have been reported, there is still no detailed research and systematic exposition specifically targeting the structure and function of the neostriatum in CD patients, which could provide valuable evidence to improve our understanding of CD.

The hypothesis of this study is that the changed structure in the neostriatum and related intrinsic connectivity could be found between CD patients and HCs using voxel-based morphometry (VBM) and seed-based FC analyses. Furthermore, based on structural and functional alterations associated with the neostriatum, the relationships could be identified between clinical data and these neuroimaging findings in CD patients. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1603/rc>).

Methods

Participants

The study consisted of 65 subjects, including 34 CD patients and 31 HCs. CD patients were recruited from the Outpatient Clinic of Gastroenterology at the Second Affiliated Hospital of Xi'an Jiaotong University. Patients with a previous CD diagnosis were contacted by registered telephone to determine whether they were willing to participate in the experiment for a certain amount of monetary compensation, while HCs were recruited through advertisement.

CD patients were assessed by illness duration, Inflammatory Bowel Disease Questionnaire (IBDQ) and CDAI (26,27). Visual analog scale (VAS) was used to evaluate the pain index. Pain was divided into 11 grades ranging from 0 (no pain) to 10 points (maximum pain).

All subjects were assessed with the Hospital Anxiety and Depression Scale (HADS) (28). HADS includes two parts: HADS-anxiety (HADS-A) and HADS-depression (HADS-D). Both HADS-A and HADS-D are composed of 7 items, and the score of each item ranges from 0 to 21 points (score ranges: normal, 0 to 7; mild, 8 to 10; moderate, 11 to 14; and severe, 15 to 21).

CD has active phase and remission phase, which are usually studied in groups in existing studies. The CD patients in this study were in remission, so patients who had an episode of CD in the past 12 months were excluded to avoid confounding the findings. The inclusion criteria were based on gastroenterologists at the Second Affiliated Hospital of Xi'an Jiaotong University and reference to existing literature. CD patients with mild disease, especially those with anxiety and depression scores of no more than 7, were included in the study to prevent the influence of comorbid factors and to reduce the potential impact of disease severity on study results. CD patients with mild disease may be more representative of the pathophysiological processes in the early stages of the disease, which would help us better understand the mechanisms of disease occurrence and progression.

The inclusion criteria of CD patients were as follows: (I) right handedness; (II) between 20 and 45 years of age; (III) education years >6 years; (IV) disease remission for more than 12 months; (V) CDAI <150; and (VI) HADS-A and HADS-D scores ≤ 7 . The exclusion criteria for CD patients were as follows: (I) patients with metal implants; (II) claustrophobic patients; (III) women in menstruation, pregnancy or lactation; (IV) patients who underwent CD-related abdominal surgery; (V) those who have a history of 5-aminosalicylic acid (5-ASA), azathioprine (AZA), or psychotropic drug use in the past 3 months; and (VI) participants with a history of neurological or psychiatric illness.

The basic inclusion criteria for HCs were as follows: (I) right handedness; (II) between 20 and 45 years of age; (III) education years >6 years; (IV) HADS-A and HADS-D scores ≤ 7 ; and (V) no abdominal symptoms, intestinal transport disorders or abdominal surgery history in the past 12 months. HCs performed a basic evaluation to ensure they did not have familial psychosis or neurological disorders and did not drink alcohol or take drugs 1 week prior. And the exclusion criteria for HCs were as follows: (I) controls with metal implants; (II) claustrophobic controls; (III) women in menstruation, pregnancy, or lactation; and (IV) those who have a history of corticosteroids, antitumor

necrosis factor alpha agent, or psychotropic drug use in the past 3 months.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All examinations were performed by specialist gastroenterologists and experienced psychiatrists in the Second Affiliated Hospital of Xi'an Jiaotong University. The Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University in China approved all of the procedures of this study (No. 2020081). Participants were informed of all experimental procedures and signed an informed consent form.

Image acquisition

Participants were scanned on a 3.0-T magnetic resonance scanner (Signa HDXT, GE Healthcare, Chicago, IL, USA) to obtain magnetic resonance imaging (MRI) data. All participants were instructed to lie on their backs along a pair of foam pads to reduce scanner noise and minimize head movement. High-resolution brain structural images were obtained with a T1-weighted three-dimensional spoiled gradient recall sequence. Sequence parameters were as follows: repetition time (TR) = 8.78 ms, echo time (TE) = 2.83 ms, field of view (FOV) = 240 mm \times 240 mm, matrix size = 256 \times 256, in-plane resolution = 0.94 mm \times 0.94 mm, slice thickness = 1.0 mm (no gaps), flip angle (FA) = 12°, and slices = 150. The resting-state functional MRI (rs-fMRI) data were acquired using a gradient-echo echo-planar imaging (EPI) sequence with the following parameters: TR = 2,000 ms, TE = 30 ms, FOV = 240 mm \times 240 mm, matrix size = 64 \times 64, in-plane resolution = 3.75 mm \times 3.75 mm, slice thickness = 3.5 mm (no gaps), FA = 90°, and slices = 43. All subjects were instructed to remain awake and relax with their eyes closed throughout the scan. For this purpose, the participants received the necessary explanation and training before the scan and were questioned after the data collection.

Structural MRI data preprocessing

All the structural images were processed using computational anatomy toolbox (CAT12) to perform VBM analyses. First, structural MRI images were reoriented to the anterior commissure by the Montreal Neurological Institute (MNI) 152 coordinate system. Next, the images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF). All gray matter images were normalized to the MNI space using the DARTEL method and modulated by

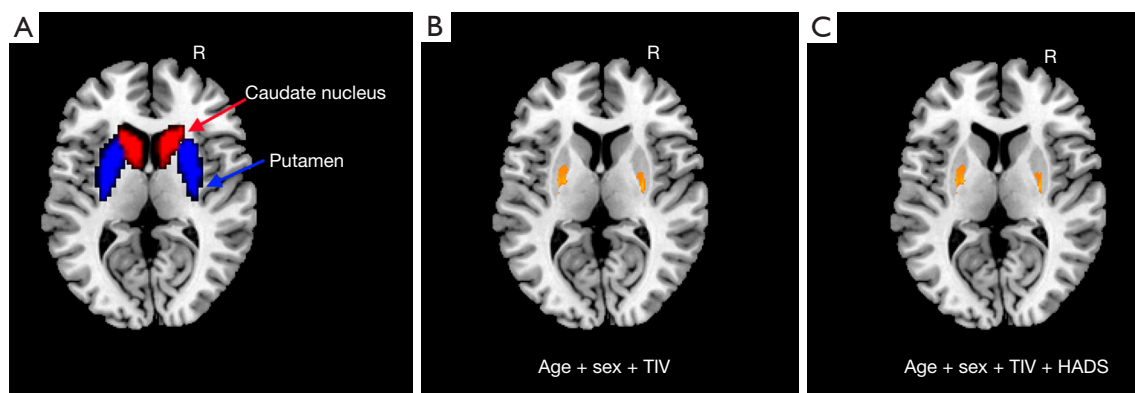


Figure 1 The GMV differences between CD patients and HCs in the bilateral neostriatum: (A) the region of the caudate nucleus and putamen bilaterally; (B) significant differences in the bilateral putamen between CD patients and HCs (covariates were age, sex and TIV); and (C) significant differences in the bilateral putamen between CD patients and HCs (covariates were age, sex, TIV and HADS). R, right; TIV, total intracranial volume; HADS, Hospital Anxiety and Depression Scale; GMV, gray matter volume; CD, Crohn's disease; HCs, healthy controls.

the Jacobian determinant of the deformation derived from the spatial normalization, avoiding bias in their intensity due to the expansion of the region during the distortion process. Last, the gray matter images were smoothed with a full width at half maximum (FWHM) isotropic Gaussian kernel of 6 mm (22,29,30).

FMRI data preprocessing

Data reprocessing of all the original functional images was performed with the Data Processing & Analysis for Brain Imaging (DPABI) toolkit (version v5.2, <http://rfmri.org/dpabi>) based on the MATLAB platform. The data underwent processing through the following steps. The fMRI data were collected at 180 volumes. To achieve magnetization equilibrium, the initial 5 functional volumes were discarded. A slice-timing correction was performed to adjust for different acquisition time of slices. Head motion correction was performed to eliminate movement artifacts in the time series. Any fMRI data with excessive head movement (translation >2 mm in any plane or rotation >2° in any direction) was discarded. All CD patients and HCs meet the above requirements. The spatial normalization of the realigned functional images into standard MNI152 space was performed using an EPI template. And the normalized functional images were resampled to 3 mm × 3 mm × 3 mm. After this, the images were then smoothed with a Gaussian kernel with a FWHM of 6 mm. Meanwhile, a regression model was utilized to eliminate

the effects of nuisance variables (including head motion parameters from the Friston 24-parameter model, white matter signals, and CSF signals) from the time series of each voxel. Global signal regression alters the distribution of signal correlations in regions of the brain and can induce artificial inverse correlations, potentially removing real neural signals. Therefore, global signal regression is not performed in this step. After detrending the time series, the filter with a bandwidth of 0.01–0.1 Hz was used to remove the interference of low-frequency drift and high-frequency physiological noise.

Statistical analysis

Demographic and clinical data

The Chi-squared test and two-sample *t*-test were applied to estimate differences in the demographic and clinical data, as well as the differences of the mean GMV of the caudate nucleus and putamen bilaterally between the two groups. All analyses were executed with SPSS 19.0 (IBM, Armonk, NY, USA). We set significance level at $P < 0.05$.

VBM analysis

We used Statistical Parametric Mapping (SPM12) (<http://www.fil.ion.ucl.ac.uk/spm>) to perform a two-sample *t*-test to test for group differences of GMV within the caudate nucleus and putamen bilaterally. The regions of the caudate nucleus and putamen bilaterally in the automated anatomical labeling (AAL) template were shown (Figure 1A).

Table 1 Clinical and demographic information of CD patients and HCs

Variables	CD (n=34)	HCs (n=31)	P value
Age (years)	30.32±4.89	30.13±3.82	0.860 [†]
Sex (male/female)	26/8	21/10	0.432 [‡]
Weight (kg)	57.12±8.10	60.01±6.89	0.127 [†]
Illness duration (months)	76.06±48.76	–	–
CDAI	69.91±39.26	–	–
IBDQ	175.90±23.39	–	–
VAS	1.23±1.79	–	–
HADS-A	6.06±2.71	3.32±2.06	<0.001 ^{†***}
HADS-D	4.44±2.93	2.87±1.93	0.014 ^{†*}

Data were expressed as the mean ± SD or number. [†], the P value was obtained by two-sample *t*-test; [‡], the P value was obtained by Chi-squared; *, P<0.05; ***, P<0.001. CD, Crohn's disease; HCs, healthy controls; CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; VAS, visual analog scale; HADS-A, Hospital Anxiety and Depression Scale-anxiety; HADS-D, Hospital Anxiety and Depression Scale-depression; SD, standard deviation.

Covariates including age, sex, and total intracranial volume (TIV) were controlled [P<0.05; cluster-level false discovery rate (FDR)]. Statistical analysis was performed again after HADS was added to the covariate.

Seed-based FC analysis

Different peak values of clusters within the neostriatum as assessed by VBM were evaluated as regions of interest (ROIs) for seed-based FC analysis. Each ROI was selected to create a sphere with a 3 mm radius. The mean blood-oxygen-level-dependent (BOLD) time course was extracted from each ROI, and its Pearson correlation with the time course of every voxel in the entire brain was computed to generate the resting-state FC map for each subject. Finally, we applied a Fisher *r*-to-*z* transformation to the resting-state FC map to improve normality, resulting in the generation of a *z*-FC map for each subject. Group differences of FC between CD patients and HCs were tested using two-sample *t*-tests by SPM12. Age and sex were entered as covariates. The FC analysis was reperformed with HADS-A and HADS-D scores as additional covariates (P<0.05; cluster-level FDR).

Correlation analysis

Different peak values of clusters within the neostriatum as assessed by VBM were evaluated as ROIs. Each ROI was selected to create a sphere with a 3 mm radius. The mean GMV was extracted from each ROI. Pearson correlation was used to detect the relationship between the average

GMV and clinical variables, including VAS, illness duration, HADS-A, and HADS-D. Age and sex were included as covariates.

Results

Demographics and clinical characteristics result

As shown in *Table 1*, there were no significantly statistical differences by age, sex and weight (P>0.05). However, HADS-A and HADS-D scores of CD patients were significantly higher (P<0.05).

VBM result

Within the identified neostriatum, group differences were found to be located in the bilateral putamen between the CD patients and the HCs {left putamen MNI coordinate: [(-24, -6, 9), P<0.001]; right putamen MNI coordinate: [(27, -9, 9), P<0.001]} (*Figure 1B,1C*). Peak coordinates of VBM results before and after regression HADS were not affected, and GMV results are shown in *Figure 2*.

FC result

The putamen-related FC results are shown in *Figure 3* and *Table 2*. Compared with HCs, CD patients had significantly decreased FC related to the left putamen-right calcarine cortex, left putamen-left fusiform gyrus, left putamen-

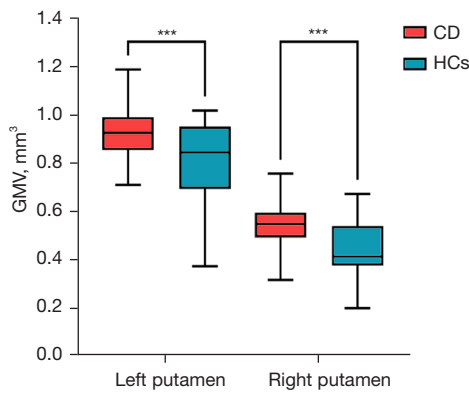


Figure 2 Comparison of GMV in CD patients and HCs at peak coordinates. Box represents the quartile range of data. The upper boundary of the box is Q3, the lower boundary is Q1, and the median inside the box is represented by a line. Whisker: a straight line extending from the upper and lower ends of the box to represent the maximum and minimum values of the data. ***, P value <0.001. CD, Crohn’s disease; HCs, healthy controls; GMV, gray matter volume.

inferior temporal cortex (ITC) as well as right putamen-bilateral parahippocampus, and increased FC associated with the right putamen-right precuneus as well as right putamen-left cuneus.

Correlation result

As shown in *Figure 4*, CD patients had a significant positive correlation between the GMV in the left putamen and illness duration ($r=0.42$, $P=0.013$). However, there was no significant correlation between the right putamen and the illness duration.

Discussion

In this study, we investigated changes of GMV and FC in the neostriatum in CD patients compared with HCs. The main findings are as follows: Compared with HCs, (I) CD patients had increased GMV in the bilateral putamen;

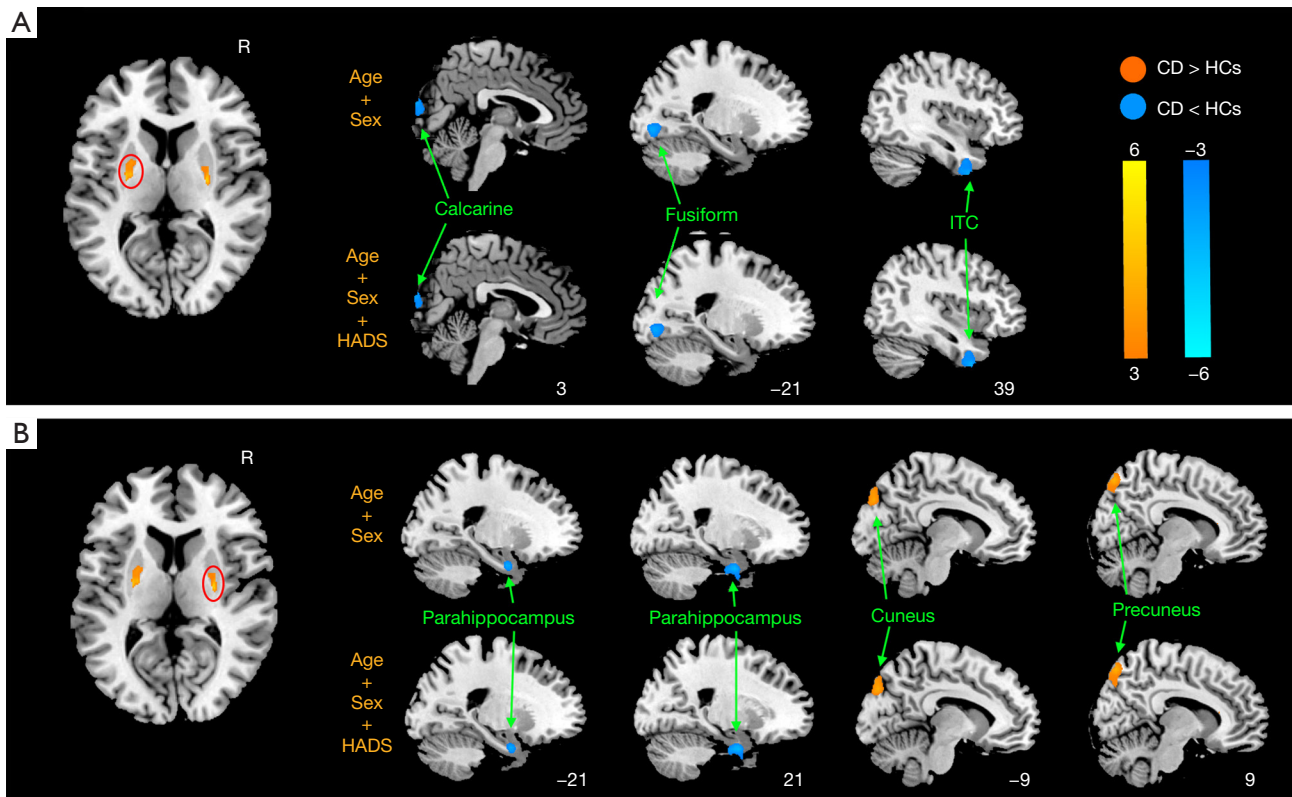
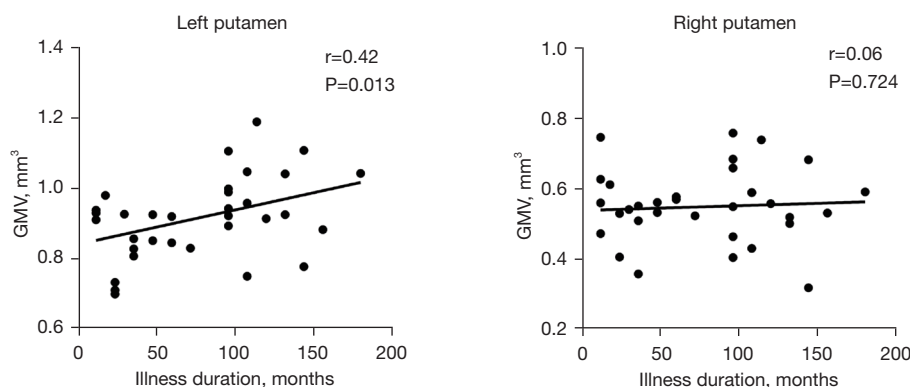


Figure 3 Brain regions with significant differences in FC between CD patients and HCs of (A) the left putamen and (B) the right putamen. Circles: the activation region where the ROIs are located. R, right; HADS, Hospital Anxiety and Depression Scale; ITC, inferior temporal cortex; CD, Crohn’s disease; HCs, healthy controls; FC, functional connectivity; ROIs, regions of interest.

Table 2 Brain regions showing significantly altered FC between CD patients and HCs

Brain region	BA	Hem	Peak MNI			Cluster size	T value
			X	Y	Z		
Seed: L putamen							
CD < HCs							
Calcarine	18	R	3	-93	12	104	-3.53
Fusiform	18	L	-21	-84	-6	63	-3.73
ITC	20	R	39	9	-45	93	-3.92
Seed: R putamen							
CD < HCs							
Parahippocampus	28	L	-21	-3	-27	67	-3.83
	35	R	21	-3	-30	79	-4.16
CD > HCs							
Cuneus	19	L	-9	-84	36	62	3.82
Precuneus	7	R	9	-75	54	82	3.95

FC, functional connectivity; CD, Crohn's disease; HCs, healthy controls; BA, Brodmann's area; Hem, hemisphere; MNI, Montreal Neurological Institute; X, Y, Z, peak coordinate in the MNI space; ITC, inferior temporal cortex; L, left; R, right.

**Figure 4** Correlation between the illness duration and GMV in the left and right putamen. GMV, gray matter volume.

(II) CD patients had significantly decreased FC related to the putamen-calcarine cortex, putamen-fusiform gyrus, putamen-ITC, putamen-parahippocampus, and increased FC associated with the putamen-cuneus/precuneus; and (III) CD patients showed a positive correlation between the GMV in the left putamen and illness duration.

Group differences in GMV between CD and HCs

In our study, the increased GMV in the putamen was found in CD patients compared with HCs. As the receiving part

of the neostriatum, the putamen contains various neuronal populations of relatively uniform density and plays a significant role in motor planning, emotional regulation as well as cognition activity. As part of the brain-gut axis, gut motor and visceral discomfort information in CD patients could activate visceral afferent neurons and transmit to the central nervous system, thereby affecting the putamen. And putamen also contains a somatotopic representation of bodily pain (31). Changed GMV in the putamen may reflect increased pain sensitivity in CD patients. Further, previous studies have revealed that the putamen-related

GMV is affected by cognition activity and is associated with the illness duration (32,33). Our results complemented the relationship between GMV in the putamen and illness duration. Combined with the evidence, it is possible that self-reflection, interoceptive stimuli, and visceral discomfort in CD patients may be affected by increased GMV in the putamen and illness duration. Notably, there were different patterns of correlation between GMV and illness duration in the left and right putamen. It may be caused by the division of labor between left and right putamen in CD patients and the connection with different brain networks. It could also involve differences in hemispheric specialization, structural connectivity, or functional roles of the putamen. And GMV in the putamen decreased significantly in patients with IBS (34). Studies indicated that ulcerative colitis (UC) patients also showed increased GMV in the putamen. This may be the characteristic that distinguishes CD and UC from other gastroenteric diseases (35).

Group differences in FC between CD and HCs

Compared with HCs, CD patients showed increased putamen-cuneus/precuneus FC in our study. The cuneus/precuneus partakes in the default mode network (DMN) (36,37). As one of the functional cores of DMN, the cuneus/precuneus is involved in higher-level cortical structures and broader functions such as information integration related to environmental perception and emotional response to pain (38,39). It also plays a role in the fields of attention and self-awareness (40,41). Meanwhile, abnormalities of the DMN have been reported several times in CD (19,42). The processing of visceral sensation information caused by CD is related to the DMN, especially to the cuneus/precuneus. The cuneus/precuneus may integrate visceral information including somatic sensory disturbance and expected pain of the gastrointestinal disease. The cuneus/precuneus responses induced by destructive stimuli may enhance processing of self-awareness. Thereby, we speculate that the increased FC putamen-cuneus/precuneus may represent abnormal perception or abnormal regulation of visceral discomfort in CD patients.

Compared with HCs, CD patients had significantly decreased FC related to the putamen-calcarine cortex, putamen-fusiform gyrus, putamen-ITC, and putamen-parahippocampus in our study. The calcarine cortex and the fusiform gyrus are inner central nodes in the DMN and visual network (43,44). The ITC is a central part of the tertiary visual association cortex and language expression

area, associated with visual perception, language, and memory functions (45,46). The parahippocampus, located in the medial temporal lobe, is the key structure for processing declarative memory (47). Damage to the orbital and optic nerves has been reported in CD patients (48). And there is evidence that CD is associated with verbal abnormalities, possibly due to pro-inflammatory cytokines (49). Gut inflammation and stress can produce damaging messages to the central nervous system, thereby prolonging or amplifying the sensitization of visceral afferents. It may cause high neuronal activity in endogenous nociceptive regulatory areas and central sensory amplification areas and could lead to occasional interruption within the temporal lobe network (50). We suppose that long-term chronic inflammation and abdominal stimulation might cause increased pressure on the optic nerve, stimulating the visual area and affecting the calcarine cortex and fusiform gyrus. In addition, existing literature shows that FC increased in the precuneus and FC decreased in the parahippocampal region are common in CD patients in the periaqueductal gray, insula and whole brain network, which is consistent with our results (22,42,51,52). This suggests the widespread alteration of DMN in CD patients and its close association with subcortical nuclei.

In our study, to a certain extent, emotional factors affected the putamen-related FC results but the impact was not significant. According to the previous studies, the structural differences among several regions including the putamen and caudate nucleus were not significant after controlling for emotional factors (anxiety and depression) (24,35). In addition, the effects of emotional factors on CD-related brain structures and functions were inconsistent (22-24,35). The relationship between the neostriatum and emotional factors in CD patients remains to be studied.

Limitations

There are several limitations in this study. First, there were no significant GMV differences emerged in the caudate nucleus. It might be due to the effects of CD being in remission. Moreover, the factors of anxiety and depression had no significant effect on the abnormality of putamen. Further studies should be applied to assess this in the future. The laterality of the putamen also needs further investigation. This will require the inclusion of different CD populations and more detailed grouping of CD patients based on emotional factors. VBM and seed-based FC analyses have inherent limitations. Whole-brain

connectivity analyses or machine learning approaches, could provide a more comprehensive understanding of brain alterations.

Conclusions

In summary, we found that CD patients had increased GMV in the bilateral putamen and changed patterns of FC based on the bilateral putamen as ROI. And CD patients had a positive correlation between the GMV in left putamen and illness duration. These imaging abnormalities might be related to aberrant patterns of DMN and visual processing area. It is indicated that the putamen might be a valuable marker to distinguish CD patients from HCs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1603/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1603/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University in China approved all of the procedures of this study (No. 2020081). All participants were informed of all experimental procedures and signed informed consent form prior to the experiment.

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