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Brain changes detected by functional magnetic resonance imaging and spectroscopy in patients with Crohn's disease

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Abstract

Crohn's disease (CD) is a chronic, non-specific granulomatous inflammatory disorder that commonly affects the small intestine and is a phenotype of inflammatory bowel disease (IBD). CD is prone to relapse, and its incidence displays a persistent increase in developing countries. However, the pathogenesis of CD is poorly understood, with some studies emphasizing the link between CD and the intestinal microbiota. Specifically, studies point to the brain-gut-enteric microbiota axis as a key player in the occurrence and development of CD. Furthermore, investigations have shown white-matter lesions and neurologic deficits in patients with IBD. Based on these findings, brain activity changes in CD patients have been detected by blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI). BOLD-fMRI functions by detecting a local increase in relative blood oxygenation that results from neurotransmitter activity and thus reflects local neuronal firing rates. Therefore, biochemical concentrations of neurotransmitters or metabolites may change in corresponding brain regions of CD patients. To further study this phenomenon, brain changes of CD patients can be detected non-invasively, effectively and accurately by BOLD-fMRI combined with magnetic resonance spectroscopy (MRS). This approach can further shed light on the mechanisms of the occurrence and development of neurological CD. Overall, this

paper reviews the current status and prospects on fMRI and MRS for evaluation of patients with CD based on the brain-gut-enteric microbiota axis.

Key words: Brain-gut-enteric microbiota axis; Crohn's disease; Functional magnetic resonance spectroscopy; Functional magnetic resonance imaging; Gut microbiota; Inflammatory bowel disease; Metabolite; Spectroscopy

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Core tip: The occurrence and development of Crohn's disease (CD) have strong links to the brain-gut-enteric microbiota axis and are associated with psychological factors such as stress, anxiety and depression. In patients with inflammatory bowel disease, studies have revealed white-matter lesions and neurologic disorders. Brain activity and biochemical changes in brain regions can be detected accurately by blood oxygenation level dependent functional magnetic resonance imaging combined with magnetic resonance spectroscopy in patients with CD. This approach can further shed light on the mechanism of occurrence of neurologic CD.

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INTRODUCTION

Crohn's disease (CD) is a chronic, non-specific granulomatous inflammatory disorder which can affect any part of the digestive tract. Most commonly, CD affects the small intestine. CD is a phenotype of inflammatory bowel disease (IBD). Geographically, CD is most prevalent in developed Western countries. However, recent epidemiologic studies definitely support a rapid increase in the incidence of CD in developing countries. Factors such as urbanization, improved sanitation, increased use of antibiotics and modern Western diets have all contributed to the rise of CD^[1,2]. Therefore; it should be highly valued that the prevalence of CD will increase in the near future.

To date, the pathogenesis of CD is not fully understood. The current dogma attributes CD to biological factors such as immune response, genetic susceptibility, intestinal dysbiosis, and external environmental factors^[3]. Many studies have demonstrated that the onset and development of CD are closely related to the intestinal microbiome, which has a strong relationship with the brain-gut-enteric microbiota axis in particular. In recent years, the mechanism of the brain-gut-enteric microbiota axis in CD patients has gained more

attention from researchers. In particular, the advent of blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) and hydrogen proton magnetic resonance spectroscopy (¹H-MRS) has allowed non-invasive detection of brain activity and biochemical changes. Using fMRI, abnormal functional activity has been detected in the cerebral cortex of patients diagnosed with CD. This paper therefore serves as a comprehensive review of the current status and prospects on MRS and fMRI for evaluation of patients with CD based on the brain-gut-enteric microbiota axis.

ROLE OF MICROBIOTA IN ONSET AND DEVELOPMENT OF CD

The microbiome refers to the microorganisms, their genomes and the local environment in the human intestine^[4]. A healthy gut microbiome is traditionally comprised of around 100 trillion species of microbes, most of which are bacteria^[5]. Interruption of the symbiotic relationship between microbiota and the gastrointestinal tract is referred to as dysbiosis, which perturbs host functions and is a precursor to disorders, such as IBD^[6,7]. As Prosberg *et al*^[8] demonstrated through a systematic review, patients with active IBD had lower abundance of intestinal flora compared to patients in remission. Furthermore, the phenotypes of CD and ulcerative colitis (UC) are distinct. Therefore, the pathogenesis of IBD involves complex interactions between the immune system, the microbiome and environmental factors in genetically susceptible individuals. Specifically, an imbalance in intestinal microflora for genetically susceptible individuals can lead to abnormal immune responses within the gut and damage in the intestinal mucosal barrier^[9]. This imbalance plays a key role in the progression of CD inflammation. In a study conducted by Erickson *et al*^[10], the ileum of CD patients was found to exhibit altered carbohydrate metabolism, bacterial-host interactions and the presence of human host-secreted enzymes. It is hypothesized that the aforementioned changes in intestinal function are directly induced by an imbalanced microbiota. This result further highlights potential targets for the treatment of IBD patients^[11].

MICROBIOTA AND ITS LINK TO THE BRAIN-GUT AXIS

The bidirectional signaling between the gastrointestinal tract and the brain is vital for sustaining homeostasis and is regulated at the neural level by both the central and enteric nervous systems. Hormonal and immunological regulations are also known to play a part. Studies^[12,13] have indicated that bacteria such as commensal, probiotic, and pathogenic bacteria in the gastrointestinal tract can activate peripheral

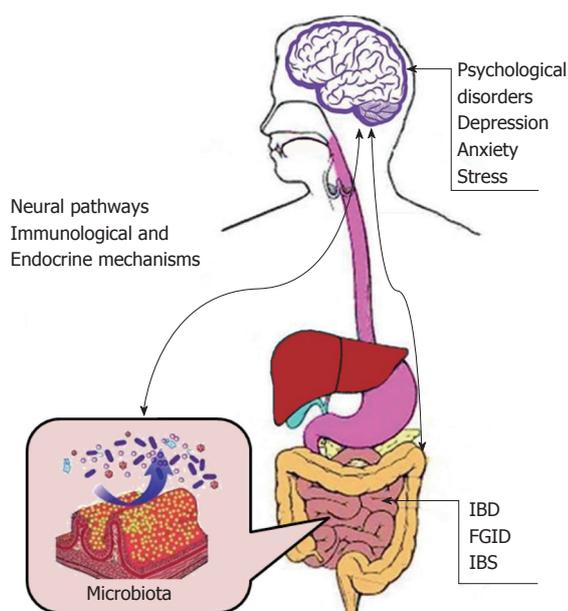


Figure 1 Brain-gut-enteric microbiota axis. The bidirectional brain-gut-enteric microbiota axis between the brain and gut involves neural pathways, immunological and endocrine mechanisms, and it is closely associated with microbiota and psychological disorders such as depression, anxiety and stress. These disorders may result in FGID, IBD and IBS. FGID: Functional gastrointestinal disorders; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome.

neural pathways and central nervous system (CNS) signaling pathways. This result is hardly surprising as the gut microbiome plays an important role in basic neuroregenerative processes such as the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation. Therefore, neural pathways in the enteric, autonomic and limbic systems along with the intestinal microbiota, immunological and endocrine systems are all regulated by the enteric microbiome. Meanwhile, the enteric nervous system is composed of small nerve cells, enteric ganglia, the nerve connectors between these ganglia, and nerve fibers that supply effector tissues. Effector tissues include intestinal smooth muscle, mucosal epithelium, intrinsic vascular and gastroenteropancreatic endocrine cells^[14]. This relationship between the brain and enteric system involving the nervous system and microbiome is known as the brain-gut-enteric microbiota axis (Figure 1). A malfunction in just one of these pathways can influence the progression of CD^[15-17].

Evidently, the enteric microbiome strongly impacts brain-gut communication in the brain-gut-enteric microbiota axis. Not surprisingly, intestinal bacterial colonization plays a major role in the development and maturation of immune and endocrine systems, which are the key factors underlying CNS signaling^[18]. Under control of the CNS, cells from the intrinsic layer of the lumen release chemokines into the intestinal lumen, which can lead to gastrointestinal motility, secretions, and changes in the intestinal permeability. All these factors perturb the gastrointestinal bacterial

environment^[19,20].

Animal studies^[21,22] have confirmed that behavioral disorders (such as stress) can change the composition of the intestinal flora. One proposed mechanism regards mucus and norepinephrine secretion by epithelial cells under stress, which results in gastrointestinal motility changes and specific strain growth. A large number of studies^[23-27] have confirmed that factors such as stress, anxiety and depression can affect the activity and recurrence of CD. Recent data suggest that gastrointestinal inflammation caused by stress may be induced upon the dysfunction of the hypothalamic-pituitary-adrenal axis. This inflammation is known to alter the interaction between bacterial and mucosal mast cells through corticotrophin releasing factor.

Current research^[28] has also confirmed that intestinal microbiota can directly alter neural biochemistry and that dysbiosis may directly contribute to mental illnesses in patients with intestinal disorders. The study compared parameters of anxiety-like behavior and motor activity between specific pathogen free mice with a normal gut microbiota and germ free (GF) mice. The GF mice exhibited decreased anxiety and increased motor activity. Further studies^[29-31] also revealed that animals with non-invasive infections with pathogens in the cecum showed rapid activation of brainstem nuclei and exhibited anxiety like behavior. This reaction is believed to be mediated by signals from the vagal afferents to the nuclei of the solitary tract and the lateral parabrachial nuclei.

These studies have proved that the occurrence and development of CD have strong links to the brain-gut-enteric microbiota axis and involve psychological factors such as stress, anxiety and depression.

BOLD-fMRI FOR DETECTION OF BRAIN CHANGES IN CD

BOLD-fMRI^[32,33] was first reported by Ogawa *et al.*^[33] in 1990, and since then, it has become a powerful method for detecting brain activity. BOLD-fMRI functions by detecting a local increase in relative blood oxygenation that results from neurotransmitter activity and thus reflects local neuronal firing rates (Figure 2). The activity of nervous system activity is therefore detected indirectly by assaying the proportion between deoxyhemoglobin and oxyhemoglobin in blood. Inspection methods are divided into the task state and resting state (rs-fMRI). The task state is further subdivided into block design and event related methods.

The resting state is characterized by behaviors such as slow breathing and minimal physical or mental activity. In the absence of design tasks, subjects are known to cooperate willingly with high consistency. Replicative measures are therefore more easily obtained in large numbers in the resting state. During the resting state, Rs-fMRI detects low frequency

Table 1 Studies of blood oxygenation level dependent functional magnetic resonance imaging and magnetic resonance spectroscopy in Crohn's disease

Ref.	Destination	Inspection	Location	Main metabolites	Results
Agostini <i>et al</i> ^[37] , 2013	Habituation to stress in CD	BOLD-fMRI (Task-state)	Brain	NA	Different neural activities in the amygdala, hippocampus, insula, putamen and cerebellar between CD patients and controls
Bao <i>et al</i> ^[38] , 2016	Brain activity in paracastic CD patients	BOLD-fMRI (Resting-state)	Brain	NA	ReHo values: Abdominal pain: insula, MCC, SMA↑, temporal pole↓; Without abdominal pain: hippocampal/ parahippocampal cortex↑, dorsomedial prefrontal cortex↓
Bezabeh <i>et al</i> ^[41] , 2001	Diagnosis in CD and UC	MRS	Colonic mucosal	Taurine, lysine, lipid, choline, creatine	The diagnostic spectral regions include taurine, lysine, and lipids
Varma <i>et al</i> ^[42] , 2007	Early screening of IBD	MRS	Colonic mucosal	Creatinine and phosphatidylcholine	Triglycerides, creatine, phosphocholine and glycerol backbone of lipids are the most discriminatory metabolites
Fathi <i>et al</i> ^[43] , 2014	Biomarkers of CD	MRS	Serum	Alanine, glutamine, leucine/isoleucine, lysine and valine	Two chemical shifts of isoleucine (0.99 ppm) and valine (1.03 ppm) have considerable impact for discriminating patient and normal samples

BOLD-fMRI: Blood oxygenation level dependent functional magnetic resonance imaging; CD: Crohn's disease; IBD: Inflammatory bowel disease; MCC: Middle cingulate cortex; MRS: Magnetic resonance spectroscopy; NA: Not available; ReHo: Regional homogeneity; SMA: Supplementary motor area; UC: Ulcerative colitis.

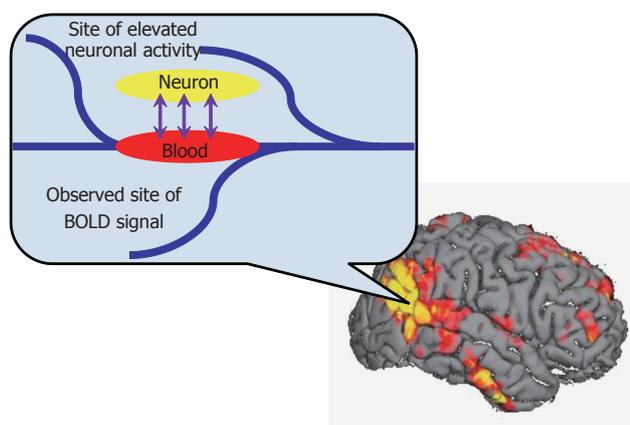


Figure 2 Mechanism of blood oxygenation level dependent functional magnetic resonance imaging. BOLD-fMRI functions by detecting a local increase in relative blood oxygenation resulting from neurotransmitter activity and reflecting local neuronal firing rates. The nervous system activity is detected indirectly by assaying the proportion between deoxyhemoglobin and oxyhemoglobin in blood. BOLD-fMRI: Blood oxygenation level dependent functional magnetic resonance imaging.

fluctuations in functional brain regions based on blood oxygen level. Rs-fMRI analytical methods include regional homogeneity (ReHo)^[34], functional connectivity (FC)^[35] and amplitude of low-frequency fluctuation (ALFF)^[36]. Using fMRI, Agostini *et al*^[37] and Bao *et al*^[38] found abnormal functional activity in the cerebral cortex of patients with CD (Table 1).

Agostini *et al*^[37] hypothesized inadequate habituation to stress as a characteristic for CD patients, and their study sought to compare neural habituation between CD patients and healthy subjects. During a high-stress task, different neural regions were activated between the two groups. Particular differences arose in the activation of the amygdala, hippocampus, insula, putamen and cerebellar regions. These contrasts revealed a stark difference in the habituation to stress between CD affected individuals and controls. Particularly, CD patients demonstrated inadequate

habituation to stress as previously hypothesized, which contribute a link between stress and exacerbated inflammation. These results suggested that the self-regulation of stress levels in CD patients is decreased, which can be an important factor in exacerbating intestinal inflammation.

Bao *et al*^[38] investigated changes in resting-state brain activity in paracastic CD patients with and without abdominal pain. Regional homogeneity (ReHo) was used to assess resting-state brain activity. They found that patients with abdominal pain exhibited lower ReHo values in the insula, middle cingulate cortex (MCC) and supplementary motor area (SMA), with higher ReHo values in the temporal pole. In contrast, patients without abdominal pain exhibited lower ReHo values in the hippocampal/parahippocampal cortex and higher ReHo values in the dorsomedial prefrontal cortex. These results showed a significant negative correlation between the ReHo values of the insular and MCC activities with the daily pain scores of patients with abdominal pain. The results of this study confirmed a difference in resting state brain activity between CD patients with and without abdominal pain. Furthermore, the abnormal activity of insular and MCC regions was closely related to the severity of abdominal pain.

MRS AND METABOLOMICS IN CD

MRS^[39] utilizes nuclear magnetic resonance phenomena and chemical shifts to quantitatively analyze specific atomic nuclei and their compounds. As a non-invasive, quantitative measurement for physiological and biochemical changes of internal organs and tissue metabolism, MRS offers unparalleled versatility and safety. Not only does MRS characterize functional groups, but describes the relationships between appropriate nuclei different constitutional isomers and stereoisomers. To date, *in vivo* MRS of the brain in CD

Table 2 Metabolites for magnetic resonance spectroscopy and their functions in normal adult human brain^[66]

Metabolite	Chemical shift (ppm)	Concentration range (mmol/kgww)	Functions
NAA	2.02	7.9-16.6 (average 10.3)	An osmolyte, a storage form of aspartate, a precursor of NAAG, a marker of neuronal density
GABA	3.01	1.3-1.9	A primary inhibitory neurotransmitter
tCho	3.20	0.9-2.5	An essential nutrient that is required for synthesis of the neurotransmitter acetylcholine, and of phosphatidylcholine, a major constituent of membranes
Cr	3.05	5.1-10.6	A concentration reference
Glu	2.04-2.35	6.0-12.5	An excitatory neurotransmitter
Gln	2.12-2.46	3.0-5.8	A precursor and storage form of glutamate
mI	3.56	3.8-8.1	An essential requirement for cell growth, and a storage form for glucose
Lac	1.33-1.35	0.4	The end product of anaerobic glycolysis

Cr: Creatine; GABA: γ -aminobutyric acid; Glu: Glutamate; Gln: Glutamine; Lac: Lactate; mI: Myo-inositol; mmol/kgww: mmol/kg of wet weight; NAA: N-acetylaspartate; ppm: Parts per million; tCho: Choline (total), free choline, glycerophosphorylcholine, and phosphorylcholine.

patients has yet to be implemented. Studies of MRS frequently use *ex vivo* samples of CD patients, such as serum/plasma, urine, stool and colonic mucosal samples (Table 1).

MRS proves useful in the study of metabolomics, which involves the high throughput analysis, characterization and quantification of small molecular metabolites. By assaying different fluids, such as serum/plasma, urine and stool samples, the presence or absence of different metabolites can be used to distinguish between IBD and healthy volunteers. MRS can even be used to discern the different subtypes (CD and UC) of IBD as metabolite changes are directly associated with changes in intestinal bacteria^[40]. These findings demonstrate that IBD is a disorder of the intestinal flora.

The differential diagnosis between CD and UC is often difficult. However, Bezabeh^[41] utilized ¹H-MRS combined with spectral data to delineate UC and CD. Tissue samples from the colon of affected patients were assayed by spectral analysis, with a 98.6% accuracy rate for discerning UC and CD. The diagnostic spectral regions include taurine, lysine, and lipids.

In another study using MRS for metabolomics, Varma *et al.*^[42] performed ¹H-MRS on *ex vivo* colonic mucosal samples for the early screening of IBD. Their results revealed differing levels of creatinine and phosphatidylcholine over time between IBD affected and healthy groups, and suggest the existence of biochemical changes in IBD.

Separately, Fathi *et al.*^[43] explored the biomarkers of metabolism in patients with CD. Using ¹H-MRS metabolic profiling of the serum samples, it was shown that valine and isoleucine levels are also useful in the differential diagnosis of CD metabolites, and these metabolites can be used for high risk screening for early diagnosis of CD patients.

CLINICAL APPLICATIONS OF MRS AND FUTURE DIRECTIONS

MRS has been most widely used in the assessment of neurologic disorders. Previous studies^[44,45] have shown

that *in vivo* quantitative or semi-quantitative detection of brain tissue metabolites including glutamine (Glu), glutamate (Gln), γ -aminobutyric acid (GABA), N-acetylaspartate, myo-inositol, choline, creatine, glycerophosphorylcholine and phosphorylcholine can indicate neurological cell density, metabolism, permeability and other factors. The functions of clinically detectable neurochemical metabolites are listed in Table 2. Therefore, *in vivo* MRS is instrumental in the diagnosis of brain diseases such as tumors, ischemia, infection, epilepsy, metabolic disorders, dementia, mental diseases and so on^[46,47]. MRS combined with clinical evaluations and conventional MRI is essential for diagnosing certain entities. Further studies^[48,49] have shown that white-matter lesions and neurologic deficits in IBD patients may be an additional extra-intestinal manifestation of this disease. Despite the versatility of MRS, however, current studies more frequently employed CD spectrum analysis of urine and fecal samples of CD patients. Meanwhile, *in vivo* MRS in the brain of CD patients has yet to be implemented.

Neurotransmitter mediated signal transduction plays an important role in the regulation of cerebral blood flow, which is mainly controlled by astrocytes^[50]. BOLD-fMRI studies have confirmed changes in local cerebral blood oxygen concentrations in patients with CD. Based on previous observations^[37,38], it is hypothesized that metabolites of functional brain areas will be changed accordingly in patients with CD. Specifically, the excitatory and inhibitory neurotransmitters associated with mental and psychological factors such as Glu and GABA^[51,52], respectively, are thought to vary. The coordination between excitatory and inhibitory neurotransmitters is the basis of regulated neuronal activity, and is correlated with the amplitude of the BOLD-fMRI signal. GABA baseline levels were negatively correlated with BOLD-fMRI signals of brain activity, and this result indicates the correlation between the BOLD-fMRI signals and GABA levels^[53].

In addition, Glu and Gln serve as major excitatory neurotransmitters. Due to their similar molecular structures, the pair is often referred to as Glx. Studies

of MRS in chronic pain^[54-56] suggested that altered levels of Glx and GABA are present in patients with chronic pain, suggesting the role of neurotransmitters in pain management. Mullins *et al.*^[57] further used ¹H-MRS to investigate changes of brain metabolites in patients scoring high on the self-assessed pain scale. Results indicated that the onset of pain can induce a dynamic increase in Glu concentration in the anterior cingulate cortex. It was also found that an increased Glu concentration was significantly related to the pain level of participants' subjective experience.

While increases in Glx are corresponded to increased pain perception, GABA^[44,58,59] is an inhibitory neurotransmitter which plays an important role with Glx in neurotransmission and pain. GABA concentration in brain tissue *in vivo* is relatively low (< 2 mmol/L), and the MRS spectrum shows strong overlap with other metabolites. Therefore, traditional MRS is not optimal for detecting GABA. In light of this limitation, the spectral editing technique MEGA-PRESS (MEscher-GARwood Point RESolved Spectroscopy)^[60] was designed to allow accurate detection of GABA. Results are encouraging and offer potential applications in the screening of neurodegenerative diseases, mental disorders, acute and chronic pain.

Functional magnetic resonance spectroscopy (fMRS) has been proposed for various applications^[61-65], especially in conditions involving psychological factors. MRS combined with fMRI is known as fMRS and can be used to detect changes in brain metabolites with high accuracy.

CONCLUSION

Current BOLD-fMRI studies have confirmed changes in local cerebral blood oxygen concentrations in patients with CD. Therefore, it is hypothesized that the level of metabolites in functional brain areas will be changed accordingly. The correlation of these changes can be related with the pathogenesis of CD. Meanwhile, the progression of CD with respect to psychological factors and symptom of abdominal pain requires further investigation. Based on the brain-gut-enteric microbiota axis, fMRS can be used to study brain activity and biochemical concentrations of key neurotransmitters, particularly Glx and GABA, in patients with CD. fMRS studies therefore offer unpatrolled versatility for evaluation of patients with CD and serve to prevent further disease progression and relieve symptoms of abdominal pain for patients suffering from CD.

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