

Magnetic Resonance Neuroimaging of Inflammatory Bowel Disease

Thamaporn Tangsujaritvijit*

Prince of Songkla University, 15 Kanchanavanit Road, Kho Hong, Hat Yai District, Songkhla 90110, Thailand

*: All correspondence should be sent to: Dr. Thamaporn Tangsujaritvijit.

Author's Contact: Thamaporn Tangsujaritvijit, MD, E-mail: thamtangtajar@gmail.com

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Inflammatory bowel disease (IBD) is a lifelong, relapsing, chronic inflammatory disease of the digestive tract that can be brought on by a number of different etiologies. Studies have shown that patients with IBD also have nervous system involvement in addition to well-known extra-intestinal symptoms like arthritis and iritis, and researchers believe that neurological lesions in patients with IBD may be an important extra-intestinal manifestation. Currently, tentative findings from studies employing magnetic resonance imaging to study the brain structure and function of patients with IBD have been made.

Keywords: Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease; Magnetic Resonance Imaging; Neuroimaging

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INFLAMMATORY bowel disease (IBD) refers to a collection of chronic relapsing inflammatory disorders that affect the digestive tract, including Crohn's disease and ulcerative colitis (UC), which have different diagnoses but comparable pathologies (1). Abdominal pain, diarrhea, blood in the stool, fever, and a number of extraintestinal signs such as arthritis, iritis, and erythema nodules are some of its prominent clinical symptoms (2). According to epidemiological research, IBD is progressively spreading across the world and is fast growing in incidence in developing nations as a result of the "Westernization" of lifestyle (3). The pathogenesis of IBD may be greatly influenced by the imbalance of the brain-gut axis, which may play a significant role in the etiology of IBD (4, 5). However, the specific underlying cause of IBD is still unclear.

The two-way "communication mechanism" between the

gut and the brain is known as the brain-gut axis. The sympathetic and parasympathetic autonomic nervous systems, the central nervous system, the stress system (i.e., the HPA axis), the gastrointestinal corticotropin (CRF) system, and the five sections of the intestinal response are its key constituents (6). Heart rate variability and cortisol concentration in serum or saliva are currently the key biological indicators to investigate the function of the brain-gut axis as a marker of sympathetic-vagal balance (7) and indicators for imaging examinations of the brain (8). Brains of IBD patients can be imaged non-invasively and *in vivo* using magnetic resonance imaging, allowing researchers to examine how the nervous system is affected.

Structural Magnetic Resonance Imaging

Voxel-Based Morphology

Voxel-based morphometry, also known as VBM, is an automated method for analyzing brain imaging that allows for morphological study of the entire brain tissue using high-resolution T1 weighted images (T1WI) (9). According to Agostini et al., CD patients have a lower volume of gray matter in their dorsolateral prefrontal cortex and the anterior section of their middle cingulate gyrus (10). The reduction in gray matter volume in the pre-frontal cortex and limbic regions may be an anatomy of the development of cognitive and emotional disorders in IBD patients, while the change in gray matter volume in the “pain matrix” in the cingulate gyrus may be related to the hyperalgesia displayed by patients. Additionally, the investigators discovered that in several neocortical and limbic regions, disease duration was negatively correlated with gray matter volume, which suggested that brain structural changes may be at least partially owing to persistent intestinal inflammation. Bao et al. discovered increased gray matter volume in some brain regions after increasing the sample size, in addition to finding lower gray matter volume in some brain regions in CD patients (11). According to his study, CD patients had significantly lower gray matter volumes in the anterior cingulate cortex, supplementary motor area, insula, postcentral gyrus, precentral gyrus, amygdala, putamen, globus pallidum, thalamus, hippocampal cortex, and cerebellar gray matter, whereas these regions had significantly higher gray matter volumes. After anxiety and depression were taken into account, it was discovered that differences in the volume of gray matter in some brain areas involved in emotional processing, such as the amygdala, vanished or decreased, suggesting that psychological factors have an effect on the gray matter structure in CD patients’ brains. In a different study by Bao and coworkers, it was discovered that individuals with stomach discomfort saw a decrease in gray matter volume in the insula and anterior cingulate gyrus while they were in remission (12). A number of other painful visceral illnesses, including irritable bowel syndrome, have been linked to similar findings in the anterior cingulate and insula, which are important parts of the medial pain system (13).

Diffusion Tensor Imaging

White matter fiber bundles are observed and tracked using diffusion tensor imaging (DTI), which assesses the integrity of the white matter microstructure (14). The analysis method known as tract-based spatial statistics (TBSS) is one of the most used ones in DTI research (15). The axial diffusion coefficients of the right corticospinal tract and right superior longitudinal tract were decreased in patients with IBD in a diffusion tensor imaging study (16). No significant variations in mean diffusivity, radial diffusivity, or fractional anisotropy were seen in IBD patients indicating that IBD patients who have milder brain lesions such as axonal damage or those who already have severe lesions (17).

The abnormal changes in brain morphology in IBD patients still could not establish a causal link between brain morphological alterations and disease start or the actual disease because of the limitations of cross-sectional studies. Patients with CD demonstrated significant abnormalities in the microstructural characteristics of language-relevant white matter tracts (18). Moreover, the microstructural alterations of CD patients

demonstrated relationships with anxiety level and disease duration (19).

Functional Connectivity

Functional connectivity, which is relevant to both resting-state and task-state fMRI research, describes the temporal correlation of activities among physically unconnected brain regions. Functional connectivity can be analyzed using a variety of techniques, although independent component analysis and seed points are the most commonly used in research (20).

Seed-Based Functional Connectivity

The most popular analytical technique is the functional connection based on the seed point. Determine the interval between the region of interest (ROI, also known as the seed area) or each ROI and the entire brain voxel by extracting the BOLD time course from the ROI. Alignment of the sequences as the primary component of the limbic system, the hippocampus can influence the stomach via a number of routes, including the HPA axis, the vagus nerve, and the immune system (21). Studies have discovered that the bilateral hippocampus-limbic system’s functional connection is decreased in IBD (22). The limbic system is regarded as a higher center for controlling visceral function, and the hippocampus is involved in controlling the immune system along with other limbic system brain structures control visceral feeling and movement (23). Lower functional connection between the hippocampus and other limbic structures may point to the limbic system’s diminished capacity to control pain and visceral experience in CD patients.

The simplicity, sensitivity, and readability of point-based functional connections make them a popular choice, but there are drawbacks as well. The choice of the seed area determines the outcomes. Multiple systems cannot be investigated at once because the results produced by various seed points differ.

Independent Component Analysis

The multivariate statistical technique known as independent component analysis (ICA) breaks down the full BOLD data set into its statistically most independent components without the requirement to choose ROI in advance (24). In a study of the functional integrity of several neural networks in CD patients in remission, Hou et al. discovered that CD patients displayed localized aberrant connections in both subsystems of the default mode network (DMN), particularly in the left subsystem (25). It has been hypothesized that the symptoms of anxiety and depression in CD patients are linked to limbic dysfunction in the ACC and MCC areas (26). The anterior and posterior cingulate cortex, anteromedial prefrontal cortex, precuneus, and bilateral subparietal regions are just a few of the cortical areas along the central axis of the brain that make up the DMN, a group of brain regions that are more active at rest than when performing a task (27). These areas are thought to be involved in affective and cognitive self-referential processes. Patients with CD display aberrant DMN connections, which is proof that the neural networks themselves are dysfunctional.

Functional Magnetic Resonance Imaging

Blood oxygenation level-dependent functional magnetic reso-

nance imaging (BOLD-fMRI), which uses variations in cerebral hemodynamics to track changes in brain neurons, is the mostly used type of fMRI detecting the local brain tissue's functional activity.

Task-Based fMRI

The fundamental technique for studying brain function is task-based fMRI. While receiving magnetic resonance imaging, patients are required to conduct pertinent task tests to determine the level of activity in the task-related brain areas. Agostini et al. used an emotional visual stimulation task to examine changes in emotional brain processing in 10 UC patients in remission and 10 healthy controls, and found that the amygdala, thalamus, and cerebellum of UC patients showed lower BOLD activation in response to positive emotional stimuli. The amygdala is crucial in the processing of emotions because it serves as the anatomical foundation for the relationship between the stomach and emotion (28). Because of the decline in its BOLD signal, UC patients are less receptive to happy feelings, which may be linked to the disease's start. Later, the de Dios-Duarte used the Stroop color word interference task to carry out two stress-induced repetition tests in order to look at how CD patients get accustomed to stress (29). The insula, thalamus, cerebellum, and medial temporal lobe (which includes the amygdala and hippocampus) were shown to have aberrant neuronal activity patterns in CD patients. These brain structures are essential for triggering and controlling stress responses, and in CD patients, their aberrant activity suggests impaired stress acclimation and insufficient stress adaptation. In the investigation into the unpredictability of rectal dilatation in CD patients, Rubio et al. discovered that, in contrast to healthy controls, CD patients had multiple brain regions active in visceral sensory processing, central autonomic regulation and cognition, emotion, and threat assessment (30). The BOLD signal of these brain regions in reaction to uncertainty was related to the patient's trait anxiety level, and responses were considerably elevated during rectal distension uncertainty. These task-based fMRIs support the linking of brain circuits that are aggravated by emotion, stress, and inflammation in IBD.

Resting-State fMRI

fMRI scanning in the resting state just requires that the person be awake, with their eyes closed, and not engaged in any cognitive processes. The patient cooperates more than that in task-state fMRI. Resting-state fMRI analysis techniques range from regional homogeneity (ReHo) to low-frequency oscillation amplitude analysis (amplitude of low frequency fluctuation, ALFF), among others, with the goal of revealing the brain's innate spontaneous activity and connectivity patterns and the topological characteristics of neural networks.

ReHo Analysis

The Kendall coefficient concordance (KCC) of each voxel in the brain tissue is calculated using the ReHo analysis method, and the consistency of a voxel with its neighboring voxels in a time series is examined (31). This shows that the spontaneous activity of neurons in nearby brain regions may exhibit aberrant synchronization or coordination. Accordingly, CD patients had ab-

normal changes in ReHo values in several brain regions, including the steady-state afferent network and the default mode network, compared to healthy individuals (32). This finding implies that CD patients' capacity for self-regulation decreased, and their bodies experienced balance disruption. In line with the findings of earlier VBM research, the ReHo values of the lobe and middle cingulate gyrus were negatively linked with the abdominal pain score, which suggests that chronic stomach pain in CD patients in remission may impact the functional activity of the brain (33).

ALFF Analysis

By evaluating the amplitude of the BOLD signal relative to the baseline, ALFF analysis can reflect the degree of spontaneous activity of each voxel in the brain. In various brain regions of CD patients, including the insula, anterior cingulate gyrus, medial prefrontal cortex, precentral gyrus, secondary somatosensory cortex, and hippocampus cortex, studies have revealed that the ALFF values are different (34). The regulation of visceral sensation (pain) and movement is controlled by these brain regions, which are all parts of the visceral sensation and pain network. The difference in ALFF values in CD patients suggests that the activity of the brain regions associated with visceral feeling has changed.

Even when several analysis techniques are employed, different conclusions are reached. However, it is currently believed that because IBD patients have long-term chronic intestinal inflammation, signals of intestinal inflammation or pain will be sent to the brain via the brain-gut axis, altering the function of nearby brain regions. Changes in the way associated brain regions operate will consequently have an impact on the onset and progression of IBD.

Magnetic Resonance Spectroscopy

The study of brain tumors, epilepsy, Alzheimer's disease, and other conditions is frequently conducted using hydrogen-proton magnetic resonance spectroscopy, also known as 1H magnetic resonance spectroscopy (1H MRS). It offers a non-invasive method for detecting metabolic and biochemical changes in living tissues and can perform quantitative analysis of compounds. The anterior cingulate gyrus was chosen as the region of interest in a study on the changes of brain metabolites in CD patients with abdominal pain in remission (35). It was discovered that patients with abdominal pain had higher levels of Glu/tCr in the bilateral anterior cingulate gyrus. A preliminary explanation for the alterations in brain metabolites in patients with CD abdominal pain throughout the remission period was offered by the positive correlation between the tCr level and pain score (36). This is in line with other research on chronic pain. Glu, the primary excitatory neurotransmitter in the central nervous system, controls the synthesis, release, and absorption of amino acids in neurons and glial cells. It is also thought to be a key glutamatergic neurotransmitter in the brain-gut axis. The emergence of intestinal disorders is linked to neurotransmitter dysregulation (37).

MRS can offer information to detect early lesions since metabolic alterations frequently occur before clinical changes in many diseases. The use of MRS is constrained to some extent by

the limited types of metabolites it can detect and the stringent shimming requirements.

Conclusion

The use of VBM, MRS, and BOLD-fMRI has demonstrated how IBD patients' numerous brain areas involved in pain, emotion, cognition, visceral sensation, etc. are structured and function. The way things work has changed. Functional changes are based on morphological changes, which in turn are based on

metabolic changes. The three work in concert to explain the pathophysiological alterations of the neurological system in inflammatory bowel disease. Of course, the sample size for current IBD research is often modest, and the majority of these studies use single-modal magnetic resonance. Future research must jointly employ multi-modal magnetic resonance technologies in addition to increasing the sample size to provide IBD neurological research. Research findings are becoming more and more trustworthy as the substrate changes. ■

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