

## Review Article

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# Linking the gut microbiota to brain dysfunction in bipolar disorder: Evidence from neuroimaging

Tingting Huang<sup>1,2#</sup>; Yanchao Huang<sup>3#</sup>; Yushan Shang<sup>1,2</sup>; Chunxiao Dai<sup>1,2</sup>; Qixiu Zhang<sup>1,2</sup>; Jian Xie<sup>1,2\*</sup>; Haisheng Zhang<sup>1,2\*</sup>

<sup>1</sup>Department of Clinical Psychology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China.

<sup>2</sup>Zhejiang Provincial Clinical Research Center for Mental Disorders, Hangzhou, China.

<sup>3</sup>Department of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou 310053, China.

#These authors have contributed equally to this work.

### \*Corresponding Author: Haisheng Zhang, MD

Department of Clinical Psychology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, No.261, Huansha Road, Hangzhou 310006, China.

Ph: 86-571-56006902, Fax: 86-571-56006902;

Email: zhanghaisheng3065@126.com

### Jian Xie, MM

Zhejiang University School of Medicine, No. 261, Huansha Road, Hangzhou 310006, China.

Email: srxjian@163.com

## Abstract

The gut microbiota can influence the brain function through a variety of ways, but its role in the etiology of Bipolar Disorder (BD) is yet unknown. The brain and the gut are linked through a communication pathway called the Microbiota-Gut-Brain Axis (MGBA). The current review aims to summarize the gut microbiota, neuroimaging endophenotype and its correlation in BD patients. The results demonstrated that patients with BD have drastically altered microbial diversity and taxonomic composition. Affective and cognitive-related neural networks dysfunction were found in BD patients. Additionally, BD-related microorganisms were discovered to be connected to BD-typical brain network functional connectivity properties. These investigations give preliminary evidence of the intimate connection between gut microbiota and brain networks in BD, which helps to elucidate the role of the MGBA mechanism in the pathogenesis of the condition.

**Keywords:** Bipolar disorder; Gut microbiota; Neural networks; MGBA.

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## Introduction

Bipolar Disorder (BD) is a prevalent chronic mental illness marked by recurrent manic or hypomanic episodes that may alternate with depressed episodes. According to the World Mental Health Survey Initiative, the lifetime prevalence of BD was 2.4%, with BD-I accounting for 0.6%, BD-II accounting for 0.4%, and subliminal BD accounting for 1.4% [1]. It results in a high disease burden and severe impairment in cognitive and social functions. However, the pathogenesis of BD remains unknown due to a lack of specific or objective biomarkers.

BD is a genetically complex disorder in which both genetic and environmental factors play a role [2]. The neurobiological reasons of BD included neuroinflammation, abnormalities in neuroplasticity, and brain dysfunction. Manic and depressed BD episodes cause the activation of neuroinflammatory pathways. Microglia release proinflammatory cytokines and neurotrophic factors during acute episodes of inflammation, lowering synaptic function and preventing the adverse effects that follow. The buildup of proinflammatory cytokines in chronic inflammation alters the neural pathways involved in mood and cognition, par-

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ticularly in the hippocampus, prefrontal cortex, and amygdala regions [3,4]. According to recent studies on the gut-brain axis, the gut microbiota play a critical role in orchestrating brain development and behavior, and the immune system is now recognized as a key regulator of these interactions [5]. The intestinal bacteria in the gastrointestinal tract regulate CNS function, behavior, and peripheral immunological responses, which may contribute to BD.

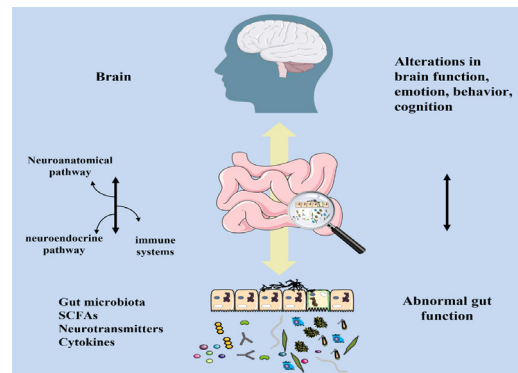
BD may be understood in the broader context of Microbiota-Gut-Brain Axis (MGBA) dysfunction based on the research that is currently available. The objective of the current review is to provide a brief introduction to the MGBA, focus on earlier research on changes in the gut microbiota in BD patients, describe the neuroimaging endophenotype in BD patients, and discuss structural and functional changes in the brain in brain-gut interactions. We go into further detail on the shortcomings of earlier research and provide possible avenues for further investigation.

### The MGBA

The human intestinal microbiota, which is made up of 10 to 100 trillion microorganisms that live in our gastrointestinal system and have a genome at least 100 times larger than our own [6]. The second genome of humans is now understood to be the gut microbiota, which is also a crucial component of human biology and a crucial environmental determinant for human health. The gut microbiota is dynamic and complex, constantly interacting with the organs and systems of our bodies and influencing host homeostasis and health status [7]. Yet, there are still gaps in our knowledge of how the gut microbiota affects brain function, particularly in humans, where it is difficult to draw conclusions from direct experiments.

The development of the brain itself in the growing infant has been shown to be influenced by the microbiota, and the brain could affect the gut microbiota and its metabolite secretion [8]. In recent years, it has been discovered that the gut and the brain interact reciprocally, leading to the concept of the MGBA. The MGBA is a significant and intricate bidirectional communication axis that connects the brain and the gut [9]. Through neural pathways, the neuroendocrine system, and the immune system, the brain can influence the gut microbiota and the release of its metabolites; conversely, the gut microbiota may produce a variety of metabolites, including short-chain fatty acids, inflammatory factors, and neurotransmitters, which either directly or indirectly control brain function through the enteric-vagus nervous system, enteric-mucosa-brain barrier, and hypothalamic-pituitary-adrenal (HPA) axis [9] (Figure 1).

The brain can influence the intestinal microbiota directly or indirectly through host-enteric microbiota signaling or by influencing the intestinal environment [10]. The sympathetic and parasympathetic nervous systems are parts of the Autonomic Nervous System (ANS), which mediates communication between the Central Nervous System (CNS) and Enteric Nervous System (ENS). This interaction can alter the physiology of the gut (muscle, mucosa, vasculature, and immune system), which in turn alters the composition and functionality of the gut microbiota [11,12]. The brain indirectly affects the gut by influencing the mucosal immune response, affecting intestinal epithelial permeability, and altering gastrointestinal secretion. The brain can regulate a variety of signaling molecules, including cat-



**Figure 1:** The microbiota-gut-brain axis. Gut microbiota, short-chain fatty acids, neurotransmitters, and inflammatory cytokines communicate with the brain through neuroanatomical, neuroendocrine, and neuroimmune pathways, altering brain function, emotion, cognition, and behavior, and vice versa.

echolamines, serotonin, dynorphin, GABA, and cytokines [13]. These neurotransmitters also have an impact on gut motility, nutrition absorption, gastrointestinal innate immunity, and gut microbiota [14]. The foundational stage for microbial colonization of the gut occurs during the first year of life, which is also the fastest and most dynamic period of postnatal brain development. Infant research revealed that alterations in the gut microbiome were related to the emergence of infant cognition [15]. According to the study, infants with higher levels of *Bacteroides* had higher cognitive scores at two years old, whereas infants with higher levels of alpha diversity had worse scores on the overall composite score, the visual reception scale, and the expressive language scale [15]. Infant neurological development and growth closely resemble the evolutionary trajectory of the infant microbiota [16,17]. Stress has been shown to impair brain growth and raise the danger of neurological and mental disorders [18]. Preclinical research showed that stress can change the composition of the gut microbiota in animal models of stress, such as mother separation [19,20]. On day 3 after separation, there were fewer *Lactobacilli* present; these alterations in the microbiome were linked to stress [20]. The abundance of the genera *Bacteroides* and *Lactobacillus* was shown to decrease in mice exposed to social stressors, while the abundance of the genera *Clostridium* rose. These changes were associated with the levels of proinflammatory cytokines [21,22].

Communication from the gut microbiota to the CNS can occur through several different pathways. The gut microbiota regulates the maturation of the immune system, the regulation of hormones (including the HPA axis), metabolic activity, and barrier function [17]. Changes in gut microbiota and decreased Short Chain Fatty Acids (SCFA), a byproduct of gut microbiota, lead to immune cell activation, such as that of macrophages, monocytes, and microglia, which may compromise the Blood-Brain Barrier (BBB) and gut and encourage immune system activation on both the peripheral and cellular levels [23,24]. The BBB integrity and brain health were revealed to be influenced by the gut microbiota and its byproducts [25]. According to a study on animals, pathogen-free mice with a normal gut microbiota showed lower BBB permeability than germ-free mice [26]. Additionally, intestinal barrier permeability and function could be influenced by the gut microbiota [27,28]. Leaky gut may be one of the underlying causes of disorders that also involve

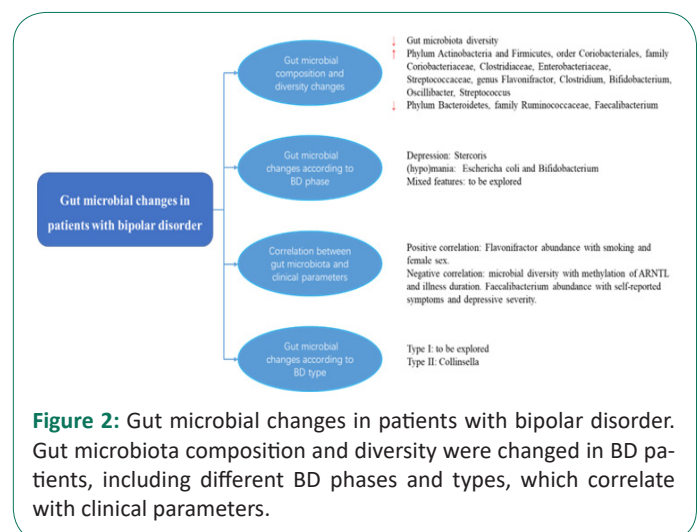
concurrent downstream BBB abnormalities [29]. The BBB acts as a semipermeable barrier to control the flow and exchange of nutrients and chemicals between the circulating blood and the brain, protecting the specific microenvironment of the CNS [30]. The BBB is crucial to brain development because it shields the growing brain from dangers outside of the body. Additionally, the gut microbiota controls brain function through the HPA axis [31,32]. The parameters of HPA axis hyperactivity have also been observed in germ-free mice in response to stress [33]. Probiotics based on *Lactobacillus* and *Bifidobacterium* have been shown to improve learning, memory, and symptoms that resemble sadness and anxiety as well as correct HPA axis dysfunction brought on by stress [34,35]. It has also been reviewed how the HPA axis mediates early life bidirectional communication between the gut microbiota and brain development [36]. According to these results, colonization of the gut microbiota is essential for controlling HPA responses and brain function. Besides, the gut microbiota regulates brain function through metabolic pathways. The bacterial metabolites SCFA and neurotransmitters including Gamma-Aminobutyric Acid (GABA), serotonin (5-HT), and dopamine, which are crucial for brain function, could be produced by the gut microbiota. Through immunological, endocrine, vagal, and other humoral pathways, SCFAs can directly or indirectly affect mood, learning, memory, and other aspects of brain function [23]. 90% of 5-HT was discovered to originate from the gut, and enteric 5-HT networks may be able to control how the adult enteric nervous system develops [37,38]. The experiment revealed that germ-free mice have an immature ENS that becomes normal after being colonized by a normal microbiota. Serotonin release was then seen to begin, followed by the activation of the 5-HT<sub>4</sub> receptor [38]. Additionally, the hippocampus of GF mice had greater concentrations of noradrenaline, dopamine, and 5-HT [39]. By controlling the metabolites of tryptophan in the gut, the gut microbiota may be able to influence brain 5-HT.

### Gut microbiota changes in BD patients

Recent research found that mental illnesses could also be understood in the wider context of MGBA dysfunction. Mental illnesses such as schizophrenia, Major Depressive Disorder (MDD), and BD were shown to alter gut microbiota traits [40-42]. In comparison to controls, BD is associated with lower levels of microbial diversity and differing relative abundances of bacterial phyla. Several investigations on humans found that BD patients have a less diverse gut microbiota [43-47]. In brief, we outlined the gut microbiome characteristics associated with mood disorders in our prior review from 2019 [48]. In these studies, it was discovered that the gut microbiota of BD patients tended to have higher levels of the phylum Actinobacteria, the order Coriobacteriales, the family Coriobacteriaceae, the genus *Enterobacteriaceae*, the lower genus *Faecalibacterium*, and the abundance of *Bacteroides*. It has been established that Actinobacteria, Coriobacteriales, Coriobacteriaceae, and *Bacteroides* are involved in the metabolism of lipids and sugars. Flavonifractor was also linked to the impact of oxidative stress and inflammatory responses [48]. Several studies have demonstrated that patients with bipolar disorder have altered gut microbial makeup. Increased abundance of phylum Actinobacteria [43,48,49] and Firmicutes [43,44,49], order Coriobacteriales [48], family Coriobacteriaceae [48], Clostridiaceae [46], Enterobacteriaceae [48], Streptococcaceae [45,47], genus *Flavonifractor* [48], *Clostridium* [43,49], *Bifidobacterium* [43,49], *Oscillibacter* [43,49], *Streptococcus* [43,49] were found in BD patients, while phylum Bacteroidetes [43,45,48], family Ruminococcaceae [45,47],

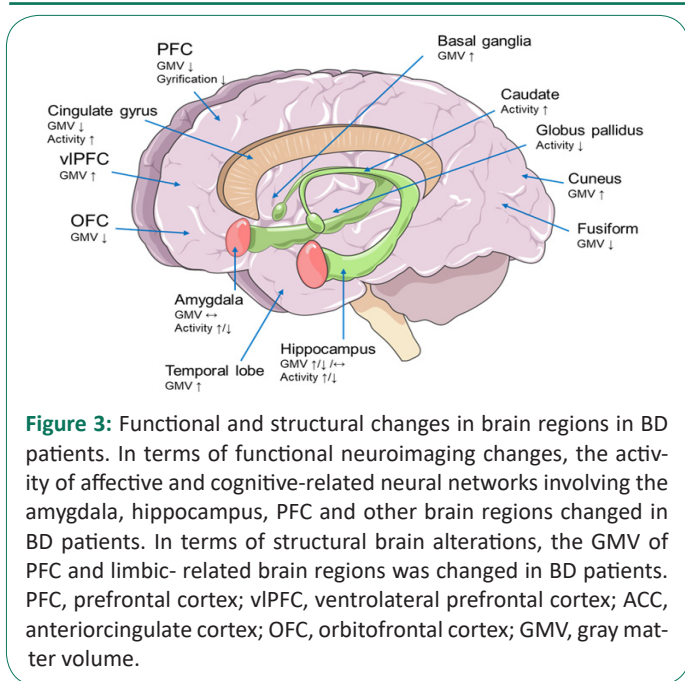
*Faecalibacterium* [48] were decreased. A reduced abundance of SCFA-producing bacteria was found in the gut microbiota of BD patients [44,50]. Clinical manifestations of BD may be partly explained by variations in gut microbiota composition. Collin-sella was found to be more prevalent in BD-II patients than BD-I patients, according to McIntyre et al [46]. According to previous research, manic BD patients had significantly higher relative levels of *Escherichia coli* and *Bifidobacterium adolescentis* than depressed BD patients, while depressed people had higher levels of *stercoris* [51]. Additionally, earlier studies in BD subjects revealed that the bacterial diversity varies between the euthymic and depressive phases, with this finding having an epigenetic effect on the circadian clock gene *ARNTL* [52]. Regarding *ARNTL* methylation, illness duration, and gut microbiome diversity, there is an unfavorable correlation [52]. The microbial bacteria *Faecalibacterium* abundance was negatively correlated with self-reported symptoms and depressive severity [53]. Furthermore, among BD patients, smoking and female sex were linked to the presence of *Flavonifractor* [54]. (Figure 2) Random forest classification models for the diagnosis and prognosis of bipolar disorder were constructed, which verified that gut microbiota could be used as biological indicators for the diagnosis and prognosis of BD [44,45]. Existing evidence has confirmed that the characteristics of the gut microbiota in BD patients have changed, but how the gut microbiota affects brain function and ultimately leads to the occurrence of BD still needs to be further studied.

### Neuroimaging endophenotype in BD patients



**Figure 2:** Gut microbial changes in patients with bipolar disorder. Gut microbiota composition and diversity were changed in BD patients, including different BD phases and types, which correlate with clinical parameters.

Up until now, MRI technology has made significant advancements in the study of mental illnesses and is frequently used in research on the neuropathological mechanisms and causes of such illnesses. Functional Magnetic Resonance Imaging (fMRI) is an indirect method to evaluate neural activity that uses a real-time blood oxygenation level dependent signal to indicate the degree of regional cerebral blood flow and oxygenation [55]. The Affective Network (AN), Default-Mode Network (DMN), Central-Executive Network (CEN), Salience Network (SN), Frontoparietal Network (FPN), Dorsal Attention Network (DAN), and Ventral Attention Network (VAN) are some of the networks that have received the most attention. The functions of these networks have been discovered to be altered in psychiatric and neurological disorders, including BD [56]. Functional and structural changes in brain regions in BD patients are shown in Figure 3.



**Figure 3:** Functional and structural changes in brain regions in BD patients. In terms of functional neuroimaging changes, the activity of affective and cognitive-related neural networks involving the amygdala, hippocampus, PFC and other brain regions changed in BD patients. In terms of structural brain alterations, the GMV of PFC and limbic-related brain regions was changed in BD patients. PFC, prefrontal cortex; vIPFC, ventrolateral prefrontal cortex; ACC, anteriorcingulate cortex; OFC, orbitofrontal cortex; GMV, gray matter volume.

### Affective-related neural networks in BD patients

Previous studies have demonstrated a close connection between the dysfunction of the emotional processing neural network and the amygdala, Dorsolateral Prefrontal Cortex (dlPFC), Medial Prefrontal Cortex (mdPFC), Ventrolateral Prefrontal Cortex (vlPFC), Anterior Cingulate Cortex (ACC), and Orbitofrontal Cortex (OFC) in mood disorders [57]. During emotional processing and regulation, amygdala activity increased; vlPFC and OFC activity decreased; and the strength of functional connections between the Prefrontal Cortex (PFC) region and the amygdala decreased in the frontal cortex [57]. Functional neuroimaging investigations have revealed abnormalities in the prefrontal cortical-amygdala-centered circuitry for emotion regulation and the prefrontal cortical-striatal reward circuitry in individuals with BD. In BD patients, both the strength of the functional connection between the amygdala and PFC as well as the activity of the emotional network in the vlPFC are greatly reduced. The vlPFC is involved in integrating emotional information, controlling emotional reaction intensity, and controlling autonomic nervous system responses to emotional stimuli. Dysfunction of the vlPFC may make it difficult to control any possible impact areas. For instance, the amygdala is connected to BD mood shift characteristics [57,58]. The amygdala and subcortical system showed an aberrant rise in activity targeted at emotional processing, which may be connected to the emotional instability seen frequently in BD patients [59]. In task-state magnetic resonance investigations, it was discovered that positive stimuli increased the activity of the vlPFC region, whereas negative stimuli lowered the strength of the functional connection between the amygdala and the vlPFC [60]. Previous studies have confirmed that during emotional processing and regulation, there is increased activity of the amygdala and/or decreased activity of the PFC, as well as abnormal functional connectivity between the amygdala and the PFC, and the value of these abnormal neuroimages is positively correlated with the severity of emotional instability, anxiety, depression, and/or mania [61].

### Neurocognitive networks in BD patients

The CEN, the DMN and the SN turned out to be the three core neurocognitive networks [56]. According to a meta-analysis of studies using whole-brain seeds to measure resting-state functional connectivity in BD patients, those with acute epi-

sodes had lower DMN seed-to-regional connectivity in the PCC and mdPFC than HCs [62]. The DMN seeds and regions of the right dorsal-anterior precuneus in the DAN, as well as parts of the left dlPFC in the FPN, also demonstrated hyperconnectivity in BD patients experiencing acute episodes [62]. When compared to cognitively normal individuals with BD who were in remission, cognitively impaired patients showed hypoactivity in the left dlPFC, frontal and parietal regions of a cognitive control network, as well as hyperactivity in the DMN [63]. According to earlier research, a hyperactive attentional style that prioritizes external stimuli over internal reflection may be the root of the hypoconnectivity between the anterior and posterior DMN in manic BD patients compared to HCs [64]. In contrast, rumination and working memory issues may be linked to the hypoconnectivity in the posterior DMN in depressive BD patients compared to HCs [65]. In BD patients, a different study demonstrated that functional connectivity between the basal ganglia and the left CEN dramatically improved, whereas it was significantly reduced between the basal ganglia and the ventral DMN/precuneus [66]. A thorough investigation revealed decreased functional connectivity between the DMN, CEN, and SN at rest [67].

### Structural brain alterations in BD patients

According to research on brain structure, BD patients have smaller amygdalas and hippocampuses, as well as less gray and white matter in their PFCs, anterior temporal lobes, and insular cortex [57]. The abnormal Gray Matter Volume (GMV) of the PFC and limbic related brain regions is related to emotional disturbance in BD depressed patients. A crucial part of the brain involved in processing cognitive and emotional information is the PFC. Affective and cognitive impairments are closely related to PFC thinning [68]. Current findings suggest neuroprogressive losses of GMV in PFC among BD patients, which are larger after first onset and with greater severity of the illness and may be associated with particular genetic characteristics [69]. The ACC is involved in cognitive and emotional tasks [70], and reduced GMV of the ACC was found both in longitudinal and cross-sectional studies in BD patients [69]. For other brain structures, increases in GMV of the temporal lobe, basal ganglia and cuneus in BD patients [69].

### Functional and structural brain alterations in brain-gut interactions

Short-chain fatty acids, inflammatory factors, neurotransmitters and other metabolites synthesized by the gut microbiota can enter the central system directly or indirectly and activate brain regions related to emotion, thus causing emotional abnormalities [71]. Animal studies have shown that feeding depressed patients' excrement to germ-free mice results in depressive-like behavior [72]. Furthermore, the use of antibiotics and probiotics significantly changed depression-like behavior in mice [73]. Additional research has demonstrated that mice kept germ-free have less anxiety-like behavior [71,74,75], and that anxiety-like behavior improved once the mice's natural intestinal microbiota structure was restored [71]. According to a study using magnetic resonance imaging and behavioral tests on germ-free mice, there are several significant differences between healthy and germ-free mice in terms of the morphology and behavior of their brain tissue. This finding suggests that gut flora is crucial for the normal growth and maturation of gray matter in various brain regions, which has significant implications for animal behavior [76]. Additionally, data from human studies demonstrates that the ACC, through its various subre-

gions, regulates emotion, behavior, the stomach and other visceral reactions. To regulate emotions, the insula combines emotional information with information from the viscera and the somatosensory system. It is connected to the control of higher order emotions and travels from the insula to the amygdala, hypothalamus, periaqueductal gray matter, and other brain stem locations. PFCs, including OFCs and dlPFC, play an important role in the regulation of emotional and visceral reactions [77]. Furthermore, two investigations split healthy groups into two groups at random. The subjects had fMRI scans before and after receiving probiotic treatment in the experimental group. Both investigations indicated that the activity of brain regions involved in central processing that regulate emotions and feelings could be seen in the probiotic group's MRI scans, indicating the role of gut flora in the control of brain function [78,79]. Studies have shown that changes in gut flora can affect changes in brain structure, such as changes in gray matter density and volume, cortical thickness, surface area, etc., in addition to their effects on brain function [80]. Taken together, these findings offer significant direct evidence for emotional control of gut sensory inputs at the level of brain anatomy and function. To characterize the microbial-gut-brain axis in BD, recent studies using gut microbial metagenomics, serum metabolomics, and neuroimaging revealed the discovery of BD-related neuroactive microbes and metabolites as potential markers associated with BD-typical features of functional connectivity of brain networks [47]. This study found that some connection networks, such as the functional connectivity of the language areas, thalamus and striatum, sensorimotor areas, hippocampus and amygdala, were related to microorganisms that were associated with neuroactive metabolites in the blood [47].

### Limitations of previous studies

Current studies have demonstrated that characteristic changes in gut microbiota, and abnormal structure and function of neural networks, and there is a close correlation between gut microbiota and abnormal structure and function of neural networks. The cause-and-effect relationship between the BD and brain-gut interactions is still not obvious, though. There are few studies that categorize the disease status of BD patients, regardless of gut microbiota or brain function studies in the condition. Patients may have variable gut microbial compositions and functional brain imaging depending on their mood condition. More studies with larger participant samples are required because there are hardly any studies that provide repeated results. Future research should go further to elucidate the relationships between gut microbiota and brain function in BD patients using multiomics approaches such as proteomics, metabolomics, radiomics, and metagenomics.

### Conclusions

There were significant alterations in the gut microbiota in BD patients, including decreased microbial diversity and composition changes, which may be related to disease phase and type. Additionally, affective and cognitive-related neural networks involving the AN, DMN, CEN, SN and other networks were altered in BD patients. BD-related microorganisms and metabolites were discovered to be connected to BD-typical brain network functional connectivity properties. This review presents investigations of the link between gut microbiota and neuroimaging in BD patients to further explore the microbiota-gut-brain axis mechanism of BD.

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