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Research Paper

Gut-Brain Axis-Mediated Cognitive Impairment in Bipolar Disorder: Mechanisms and Therapeutic Implications

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ABSTRACT

Gut-brain axis dysfunction can have long-term repercussions on cognitive function and psychosocial well-being in individuals with bipolar disorder. Gut microbiota alterations are a key factor affected by this dysfunction, as they contribute to neuroinflammation, neurotransmitter imbalances, and blood-brain barrier permeability associated with cognitive deficits. Adults with bipolar disorder often experience persistent cognitive impairments, resulting in functional limitations. The objective of the study was to review existing research on the relationship between gut-brain axis dysfunction and cognitive impairment in bipolar disorder. A secondary research design using a narrative literature review was adopted. Peer-reviewed articles and scholarly sources were collected from databases such as Google Scholar and PubMed. Relevant studies were analyzed thematically. An assessment of the existing evidence reveals a consistent unfavorable link between gut dysbiosis and cognitive impairment in bipolar disorder. Individuals with bipolar disorder exhibit reduced microbial diversity, decreases in beneficial bacteria like Faecalibacterium, Prevotella, and Roseburia, and increases in pro-inflammatory taxa, leading to deficits in attention, processing speed, memory, and executive function. According to research, addressing gut dysbiosis through probiotics, psychobiotics, and anti-inflammatory diets correlates with reduced inflammation, improved cognitive resilience, decreased neuroinflammation, and enhanced post-treatment functioning.

Keywords: *Gut-brain axis, Gut microbiota, Bipolar disorder, Cognitive impairment, dysbiosis*

Bipolar disorder, once called manic-depressive illness, is a serious mental health condition that lasts a long time. It causes significant changes in mood, energy, activity levels, and thinking. About 1 to 3% of people worldwide have bipolar disorder, making it an important public health issue. This condition greatly affects how people function and their quality of life. It also places a burden on society.

The disorder has noticeable mood episodes. These can include emotional highs, known as mania or hypomania, and emotional lows called major depressive episodes. The intensity and duration of these mood changes go far beyond the normal ups and downs that most

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people experience. They can seriously disrupt a person's social life, work performance, and daily activities.

A manic episode is a time of unusually high, expansive, or irritable mood, along with increased energy and activity levels. During these episodes, people might feel extremely happy, euphoric, or unusually irritable. Common signs include heightened self-confidence, a reduced need for sleep, fast speech, racing thoughts, being easily distracted, and more goal-directed behavior. Judgment and insight often decline, which can lead to risky actions like reckless spending, unsafe sexual practices, or hasty business decisions. In severe cases, mania may involve psychotic features like delusions or hallucinations, marking a break from reality that often requires hospitalization.

Hypomania has similar symptoms to mania but is less intense and shorter in duration. Although hypomanic episodes may not cause major problems or require hospitalization, they still show significant changes from a person's usual behavior and can progress to full manic or depressive episodes if not treated.

Major depressive episodes in bipolar disorder involve a lasting low mood, feelings of emptiness or hopelessness, and a marked loss of interest or pleasure in activities that once brought joy. Other symptoms include fatigue, changes in appetite and weight, sleep issues, changes in movement, difficulty concentrating, indecisiveness, excessive guilt, and recurring thoughts of death or suicide. These depressive symptoms are often severe enough to greatly impact daily life, relationships, and work or school performance.

The classification of bipolar disorder includes several types based on the nature and severity of mood episodes. Bipolar I Disorder is diagnosed after a person has at least one manic episode, which may be followed or preceded by depressive or hypomanic episodes. Manic episodes in Bipolar I can be severe and may include symptoms of psychosis. Bipolar II Disorder involves at least one major depressive episode and at least one hypomanic episode, but no full manic episodes occur. While hypomania is less severe than mania, Bipolar II Disorder is not a milder condition because depressive episodes are often more frequent and last longer. Cyclothymic Disorder features chronic mood changes, which include many periods of hypomanic and depressive symptoms that do not meet the full criteria for hypomanic or major depressive episodes. This condition lasts for at least two years in adults. Other categories include other specified and unspecified bipolar and related disorders, which cover bipolar-like presentations that do not fully meet diagnostic criteria or are related to substance use, medications, or medical conditions.

Bipolar disorder can develop at any age, but it is most often diagnosed during adolescence or early adulthood. In younger individuals, symptoms may appear differently than in adults. They may experience quicker mood changes, irritability, and behavioral issues that can complicate diagnosis, as these symptoms can overlap with other developmental or psychiatric conditions. The disorder significantly impacts various aspects of life, including mental and physical health, relationships, education, and work performance. Conditions like anxiety disorders, substance use disorders, and psychotic symptoms often occur alongside bipolar disorder, adding to the complexity of its course and treatment.

While bipolar disorder is a lifelong condition, it is highly treatable through effective management. Successful treatment typically includes a mix of mood-stabilizing medications,

antipsychotic drugs, and therapy methods like cognitive-behavioral therapy or psychoeducation. With the right treatment, regular follow-up, and strong social support, many individuals with bipolar disorder can manage their symptoms well, reduce the chance of relapse, and lead fulfilling lives.

Cognitive impairment has been recognized as an important feature of bipolar disorder rather than just a result of acute mood episodes. Research shows that about 60-70% of people with bipolar disorder experience measurable cognitive deficits, even during stable mood periods when symptoms are minimal or absent. This suggests that cognitive issues often persist regardless of mood changes and may be a lasting aspect of the disorder. The cognitive areas most affected include memory—especially verbal and working memory—attention, processing speed, and executive functions. Executive dysfunction appears as challenges in planning, problem-solving, decision-making, mental flexibility, and self-control. These impairments tend to remain stable over time and can be seen across various subtypes of bipolar disorder, including Bipolar I and Bipolar II.

Experiencing cognitive deficits during stable mood phases has important clinical implications. Even when mood symptoms are well managed, individuals might still face functional challenges in school, work, and social situations. Cognitive impairment is closely linked to lower psychosocial functioning, poor job performance, strained relationships, and reduced quality of life. Despite the significant burden of cognitive dysfunction, there are no recognized treatments that effectively address this issue, creating a substantial gap in the management of bipolar disorder.

In recent years, researchers have recognized the gut-brain axis as an important factor in understanding how neuropsychiatric disorders develop, including bipolar disorder. The gut-brain axis is a complex network that facilitates communication between the gastrointestinal tract and the central nervous system. This happens through various pathways, including neural, endocrine, immune, and metabolic systems. The gut microbiota, which consists of trillions of microorganisms in the gastrointestinal tract, plays a key role in this communication.

It affects brain function and behavior by producing different metabolites, neurotransmitters, and neuroactive compounds. Recent studies show that the microbiota in individuals with bipolar disorder is significantly altered. This change is marked by lower microbial diversity and specific shifts, including reductions in beneficial bacteria like Faecalibacterium, Prevotella, and Roseburia, along with increases in pro-inflammatory types. These changes in microbes have been linked to cognitive impairment, driven by neuroinflammation, disruptions in neurotransmitters, and problems with the blood-brain barrier.

Understanding how the gut-brain axis influences bipolar disorder opens exciting possibilities for new treatments that focus on gut health to improve cognitive function. This review aims to summarize the current findings on gut-brain axis issues in bipolar disorder. It will look at how changes in gut microbiota relate to cognitive impairment and assess the potential for gut-focused therapies. By bringing together evidence from studies on microbes, inflammation, neuroimaging, and clinical treatment, this review will help clarify this growing research field and suggest directions for future research.

REVIEW OF LITERATURE

Multiple studies have shown significant changes in the gut microbiota of people with bipolar disorder. Yassin and colleagues (2025) conducted a review indicating that gut dysbiosis is a key factor in brain health for those affected. They identified specific microbial changes, such as a decrease in beneficial organisms like Faecalibacterium and an increase in pro-inflammatory taxa. Similarly, Zhang and colleagues (2022) summarized the gut microbiota composition and changes in patients with bipolar disorder. They noted that cognitive dysfunction is an important aspect of this chronic illness. Tang and colleagues (2025) further examined the gut microbial structure in these patients. They found bacteria linked to glucose metabolism, specifically Prevotella, Faecalibacterium, and Roseburia. These bacteria were connected to cognitive impairment test scores. Their experimental work involved fecal microbiota transplantation from cognitively impaired patients to mice. This showed that gut microbiota can lead to memory deficits and reduced synaptic plasticity in the prefrontal cortex. This provides direct evidence of the causal link between gut dysbiosis and cognitive decline.

Chronic low-grade inflammation has emerged as a key factor that connects gut dysbiosis to cognitive impairment in bipolar disorder. Guo and colleagues (2024) studied the relationship between gut microbiota, inflammation, and brain function in unmedicated patients with bipolar disorder II. They found that an increase in pro-inflammatory bacteria and higher systemic inflammation were linked to abnormal brain activity in areas like the cerebellum. This contributed to slower processing speed and attention issues. Generoso and colleagues (2021) reviewed the signaling between the gastrointestinal tract and the central nervous system. They noted that microbial components and metabolites can trigger the host's immune system, leading to neuroinflammation. They highlighted that while probiotics helped manage manic symptoms, they also reduced cognitive reactivity to sadness in stable bipolar patients. Altamura and colleagues (2024) systematically reviewed inflammatory biomarkers, cognitive function, and changes in brain imaging in bipolar disorder. Their findings linked chronic inflammation, indicated by cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), to cognitive deficits. They suggested that levels of C-reactive protein (CRP) are strong indicators of executive dysfunction and processing speed problems. These issues are often related to reduced grey matter volume in the prefrontal cortex.

Recent evidence has emphasized the role of blood-brain barrier (BBB) dysfunction in cognitive deficits in patients with bipolar disorder. Millett and colleagues (2025) examined how BBB hyperpermeability contributes to cognitive deficits. They gathered evidence showing that chronic low-grade inflammation causes leaky barriers, allowing peripheral toxins into the brain. This disrupts cognitive functions like processing speed, attention, and executive function. Neuroimaging studies have revealed structural brain abnormalities in patients with bipolar disorder that are linked to cognitive impairment. Bin Li and colleagues (2025) performed an observational structural MRI study on amygdala subregion volumes in major depressive disorder and bipolar disorder II. They found significantly reduced volumes in the basolateral and cortical subnuclei of the amygdala in both groups. These reductions were moderately correlated with difficulties in attention and language, reinforcing the link between amygdala atrophy and cognitive-affective dysfunction in mood disorders.

Therapeutic interventions aimed at gut microbiota have shown promise in improving cognitive symptoms in bipolar disorder. Obi-Azuike and colleagues (2023) conducted a

systematic review. They found that probiotic supplementation led to significant improvements in both depressive symptoms and cognitive impairments among patients. They concluded that repeated emotional episodes are linked to a gradual decline in cognitive and executive function, with evidence connecting cognition and gut microbiota. Sallem and colleagues (2022) studied the gut-brain axis in mood disorders. They argued that neuroactive molecules from gut bacteria influence signals affecting neuropsychiatric patterns, including mood and cognition. Their review acknowledged a strong connection between microbiota and mental disorders. They suggested that therapies focusing on gut health could clarify how this axis impacts cognitive function.

Dietary changes have gained attention as factors that can influence outcomes in bipolar disorder through gut-brain axis mechanisms. Marano and colleagues (2025) explored the effects of dietary patterns on bipolar disorder through biological pathways. They noted that gut dysbiosis, marked by reduced microbial diversity, could signal disease activity. They found that following anti-inflammatory diets, such as the Mediterranean diet, is linked to lower systemic inflammation and improved cognitive function in patients. The gut-brain axis operates through multiple communication routes. Góralczyk-Bińkowska and colleagues (2022) reviewed these pathways in psychiatric conditions. They noted that in bipolar disorder, cognitive and communication disorders relate to significant limitations in social skills. They emphasized that changes to the intestinal microbiota in patients indicate a strong connection between dysbiosis and disease progression, including cognitive factors.

METHODOLOGY

Aim

To review and summarize the evidence on how gut-brain axis dysfunction impacts cognitive impairment in people with bipolar disorder.

Objective

- To study changes in gut microbiota composition in patients.
- To investigate the effect of gut-brain axis dysfunction on cognitive impairment in bipolar disorder.
- To better understand how gut microbiota alterations affect cognitive and neuropsychiatric processes connected to bipolar disorder.

Rationale of the study

Bipolar disorder affects about 1 to 3% of the global population. It is a major public health issue because it seriously impacts individual functioning and quality of life. Cognitive impairment influences around 60 to 70% of people with bipolar disorder. This problem continues even during stable mood periods and significantly affects daily functioning, work performance, and relationships. Although there are medications for mood symptoms, no effective treatments specifically address cognitive deficits in bipolar disorder. This creates a significant clinical gap.

Recent research emphasizes the gut-brain axis as an important factor in neuropsychiatric disorders, including bipolar disorder. The two-way communication between gut microbiota and the brain involves neural, immune, and metabolic pathways that influence mood, thinking, and behavior. Studies consistently show changes in gut microbiota among patients with bipolar disorder. These changes link to cognitive deficits through inflammation and

neurotransmitter mechanisms. Thus, focusing on the gut-brain axis offers a new treatment approach.

This review aims to bring together the growing but scattered literature on gut-brain axis dysfunction in bipolar disorder. It will provide an understanding of current evidence, mechanisms, and treatment implications. By consolidating findings from studies on microbes, inflammation, neuroimaging, and clinical interventions, this review seeks to guide future research and the creation of new treatment strategies for cognitive impairment in bipolar disorder. The rationale also reflects the need to address the serious issues caused by cognitive dysfunction, which remains a major factor in long-term functional impairment despite adequate treatment of mood symptoms.

Research Design

The current study used a secondary research strategy using a narrative literature review technique. This design was selected to synthesise existing research findings and discover trends, inconsistencies, and study gaps related to gut-brain axis dysfunction and cognitive impairment in bipolar disorder.

Source of Data

Data were obtained solely from secondary sources, which included peer-reviewed research articles, systematic reviews, meta-analyses, books, or trustworthy organisational reports. To find relevant literature, we employed electronic databases such as Google Scholar, PubMed, PsycINFO, and ResearchGate.

Data Analysis

This selected literature was evaluated methodically and thematically. Key findings were reviewed and synthesised to uncover shared trends, discrepancies, and gaps in previous studies. No statistical analysis was done because the study relied only on previously available data.

DISCUSSION

The findings in this review highlight the complex relationship between changes in gut microbiota and cognitive impairment in bipolar disorder. Research by Rashnaei and colleagues (2023) examined the gut microbiota profile in Iranian bipolar disorder patients. They found that imbalances in metabolites, such as gamma-aminobutyric acid (GABA) and short-chain fatty acids (SCFAs) from gut bacteria, disrupt gut-brain axis signaling and affect cognitive function. Dai and colleagues (2022) looked into how gut microbial imbalances impact cognitive function in bipolar disorder. They identified neuroinflammation and neurotransmitter imbalance as key pathways. These results align with the work of Rosenblat and colleagues (2017), who studied inflammation as a biological basis for cognitive impairment in bipolar disorder. They pointed to the gut-brain axis as a promising area for new treatments. The authors mentioned cases where changing gut inflammatory cytokines improved psychiatric symptoms, suggesting a two-way relationship between peripheral inflammation and brain function.

Paton and colleagues (2023) explored how environmental factors interact with physiological barriers to influence cognitive ability. They emphasized that the gut barrier plays a vital role in how environmental signals affect brain health through the hypothalamic-pituitary-adrenal (HPA) axis and immune system. Their research suggests that strengthening these barriers

may help reduce the negative impact of environmental stressors on cognition. Zainal Abidin and colleagues (2025) studied psychobiotics, which are probiotics and prebiotics that affect mental health. They gathered evidence showing that certain bacterial strains can reduce systemic inflammation and depressive behaviors. Notably, they found that some atypical antipsychotics may improve the gut microbial ecosystem, presenting new treatment options for mental health. Yassin and colleagues (2025) noted that specific probiotics, like Bifidobacterium, can help reduce cognitive decline and neuroinflammation by increasing brain-derived neurotrophic factor (BDNF) and restoring gut barrier integrity.

Lin and colleagues (2024) conducted the first bibliometric analysis of publications related to bipolar disorder and gut microbiota. They identified key research areas, including the links between the microbiome and the brain, as well as treatments that change microbiota. These treatments significantly improve cognitive issues and depressive symptoms. Severance and colleagues (2020) looked at biomarkers of the microbiome and the gut-brain axis in psychiatric disorders. They discussed how changes in the gut, like inflammation and translocation, connect to cognitive outcomes. They found that people with bipolar disorder who tested positive for Candida albicans yeast experienced more severe cognitive impairments. This implies that certain harmful microbes might directly contribute to cognitive decline. Paniagua and colleagues (2026) studied metabolic, inflammatory, and intestinal permeability biomarkers related to working memory issues in outpatients with bipolar disorder and schizophrenia. They discovered that while markers of intestinal permeability were related to metabolic factors, they were not independent predictors of cognitive impairment. Instead, abdominal obesity and high glycohemoglobin levels emerged as significant predictors.

Animal studies have provided important insights into gut-brain axis dysfunction in bipolar disorder. Liu and colleagues (2025) found that prenatal exposure to valproic acid leads to a lasting reduction of SCFA-producing bacteria in offspring. This triggers microglial activation in the hippocampus and prefrontal cortex, resulting in significant memory deficits and poor carbohydrate metabolism. Wu and colleagues (2025) used artificial intelligence and neuroimaging to investigate the gut-brain axis in psychiatric disorders. They noted that in bipolar disorder, low levels of gut microbes like Akkermansia are associated with atrophy in the limbic system and changes in brain network connectivity. This sheds light on pathways linked to cognitive deficits. Krothapalli and colleagues (2024) suggested using quantitative electroencephalography (EEG) together with gut microbial analysis to create non-invasive screening tools for cognitive impairment. They explained how inflammation caused by gut dysbiosis leads to changes in brain oscillations, particularly an increase in slow-wave theta power. This increase acts as a physiological marker for cognitive decline.

Paniagua and colleagues (2025) conducted their study to compare short-chain fatty acids (SCFAs) from the gut microbiome in patients with bipolar disorder and those with schizophrenia. The researchers found that fecal SCFA levels did not correlate with cognitive scores in the bipolar disorder group. This research shows that the relationship between microbial metabolites and cognitive function is more complex than scientists previously thought. A systematic review in the Journal of Clinical Medicine (2020) looked at the link between oral and gut microbiomes and mental health. The study found that microbial signatures are connected to four main disorders, including bipolar disorder and cognitive impairments. The findings suggest that medical professionals should use specific microbiomes as diagnostic tools. Cai and colleagues (2023) explored how gut microbiota

affects neuropsychiatric disorders. They reported that current research shows imbalances in gut microbes can lead to the development of bipolar disorder and cognitive decline.

Zhao and colleagues (2024) researched how mood disorders create links between gut microbiota and brain function. They found that both major depressive disorder and bipolar disorder pose higher global health risks, leading to significant cognitive decline due to disruptions in gut-brain communication. The review showed that patients with bipolar disorder have lower alpha diversity levels compared to healthy individuals. Gut microbiota affects brain function and behavior through three pathways: neural, immune, and metabolic systems. Su and colleagues (2026) studied how gut microbiota contributes to dementia-related complications, including bipolar disorder and other mental diseases caused by gut imbalances. The researchers highlighted the potential benefits of consuming prebiotics and probiotics

SUMMARY AND CONCLUSION

This review has looked at the new evidence connecting gut-brain axis problems to cognitive issues in bipolar disorder. It shows a complex, two-way relationship that provides new insights into how the disease works and where treatment opportunities lie. The literature shows that people with bipolar disorder have important changes in gut microbiota. These changes include lower microbial diversity and specific taxonomic shifts. There are decreases in helpful bacteria like Faecalibacterium, Prevotella, and Roseburia, along with increases in harmful bacteria that cause inflammation. These changes in gut bacteria are linked to cognitive problems in areas such as attention, processing speed, memory, and executive functioning.

The evidence strongly suggests that inflammation is a key factor in the relationship between gut dysbiosis and cognitive impairment. High levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-6, as well as increased C-reactive protein levels, have been consistently linked to cognitive issues and changes in brain structure. These include decreased grey matter volume in the prefrontal cortex and atrophy of the amygdala. The loss of blood-brain barrier integrity worsens these effects by allowing toxins and inflammatory substances from the body to enter the central nervous system, which increases neuroinflammation and cognitive decline.

Therapeutic remedies that focus on the gut-mind connection provide new hope for people with bipolar disorder. Probiotic supplements have shown that they can help improve both depressive symptoms and cognitive function. Psychobiotics may also reduce inflammation in the body and affect neurotransmitter systems. Changing diets, especially by following patterns like the Mediterranean diet, can enhance cognitive function by influencing the variety of gut bacteria and the production of metabolites. Identifying specific bacteria and metabolites that impact brain function can lead to more personalized treatment options.

However, there are several challenges to consider. Most studies are observational, and we need to learn more about how changes in gut microbiota relate to cognitive issues through long-term and intervention research. Differences in study designs, methods, and patient groups make it difficult to compare results directly and apply findings broadly. Furthermore, we still need to determine the best composition, dosage, and duration of treatments aimed at the microbiota through thorough clinical trials.

This assessment highlights the intestine-brain axis as an important pathway for understanding cognitive impairment in bipolar disorder. The combination of microbial, inflammatory, and neurostructural findings provides a strong basis for developing new treatment methods that focus on gut health to improve cognitive outcomes. The evidence shows that gut dysbiosis, chronic infection, and blood-brain barrier dysfunction all contribute to cognitive deficits in individuals with bipolar disorder.

The scientific implications of these findings are significant. Cognitive impairment is a key factor affecting daily functioning and quality of life in bipolar disorder, yet current treatments do not adequately address this issue. Gut-focused approaches, including probiotics, psychobiotics, and dietary changes, offer promising additional strategies that could work alongside existing drug treatments. As the field progresses, interventions targeting the microbiota may also help reduce the substantial impact of cognitive deficits, ultimately improving the quality of life for affected individuals.

Future research should prioritize large-scale longitudinal studies to establish the timing of relationships between gut dysbiosis and cognitive decline. Additionally, randomized controlled trials should investigate the effectiveness of different probiotic strains and dietary interventions. Combining multi-omics approaches that include microbiome, metabolome, and neuroimaging data may also lead to a deeper understanding of gut-brain interactions in bipolar disorder. Furthermore, exploring individual differences in microbiota composition and response to treatments could help create personalized therapeutic strategies.

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Conflict of Interest

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