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Role of Gut Microbiota in The Development of Psychiatric Disorders (A Review)

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Abstract

Introduction: The human gut microbiota plays a pivotal role in maintaining not only physical but also mental health. Emerging evidence highlights its influence on brain development and function through the gut-brain axis. Disruption of this communication system has been linked to various psychiatric disorders.

Objective: This review aims to explore the relationship between gut microbiota and the development of psychiatric disorders such as depression, anxiety, autism spectrum disorder (ASD), and schizophrenia. It also evaluates the therapeutic potential of microbiota-targeted interventions.

Methodology: A comprehensive review of current literature was conducted using scientific databases including PubMed, ScienceDirect, and Google Scholar. Studies involving both animal models and human subjects from the last 10 years were analyzed to understand the role of gut microbiota in psychiatric conditions.

Results: Different psychiatric disorders are associated with specific gut microbial profiles. Depression correlates with reduced Bifidobacterium and Lactobacillus; anxiety with altered microbiota in germ-free mice; ASD with increased Actinobacteria and Erysipelotrichi; and schizophrenia with Collinsella and Corynebacterium. Modulating gut microbiota through probiotics, prebiotics, or fecal microbiota transplantation has shown promising outcomes in reducing psychiatric symptoms. However, more human-based studies, particularly on anxiety, are needed.

Conclusion: The gut-brain axis plays a vital role in psychiatric health. Understanding gut microbiota's influence on mental disorders opens avenues for novel therapeutic interventions. Future research should focus on personalized microbiota-based treatments to manage psychiatric conditions effectively.

Key Words: Gut-brain axis, Microbiota, Psychiatric disorders, Probiotics, Mental health

Introducton

The human gastrointestinal tract hosts trillions of microorganisms, collectively known as the gut microbiota, which play a crucial role in maintaining overall health (1). Recently, there has been growing scientific interest in the gut-brain axis, a term used to describe the bidirectional communication network between the gut microbiota and the brain (2). Emerging research suggests that gut microbiota may influence the onset and progression of various psychiatric disorders, including depression, anxiety, schizophrenia, and autism spectrum disorder (ASD) (3).

The microbiome is an increasingly prominent area in biomedical research, particularly for its implications in mental health. Through the gut-brain axis, the gut microbiota interacts with the central nervous system (CNS), producing metabolites such as short-chain fatty acids (SCFAs), including butyrate, which may influence host metabolic and neurological functions. Investigating the role of gut microbiota in psychiatric conditions like bipolar disorder (BD) may help identify novel biomarkers and inform new treatment strategies.

Studies have revealed notable differences in the composition and diversity of gut microbiota in individuals with depression when compared to healthy controls. Additionally, disturbances in gut microbiota have been associated with other mental health conditions, such as eating and sleep disorders (4). Psychiatric illnesses negatively affect an individual's ability to perform daily functions and social roles. This is especially evident in disorders such as ASD, psychosis, and mood disorders, where impairments in emotional regulation, cognition, and communication significantly hinder overall functioning (5).

Psychiatric disorders are influenced by a complex interplay of psychological, genetic, and environmental factors. Recent evidence points to a strong connection between gut microbiota and overall health, suggesting that the microbiota may play a role in the pathogenesis of several multifactorial disorders, including those related to mental health (6). The term "microbiota" refers to the community of microorganisms residing in a particular environment. In the human gut, this includes more than 10^{14} microbes, predominantly anaerobic bacteria, as well as yeasts, fungi, and viruses. This indicates that prokaryotic cells in the human body outnumber eukaryotic cells by a factor of ten (7).

The relationship between gut microbiota and various neurological and psychiatric disorders offers potential for identifying unique or overlapping microbial patterns among these conditions. This opens new avenues for understanding disease mechanisms and developing targeted therapies such as probiotics, dietary interventions, and fecal microbiota transplantation (FMT) (8). Current research continues to explore the significant associations between neuropsychiatric and neurodegenerative disorders and shifts in gut microbial composition and metabolic activity, emphasizing the importance of the gut-brain axis. The predominant bacterial phyla in the human gut microbiota are Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, and Verrucomicrobia (9).

Recent findings also highlight that the development of the gut microbiome occurs concurrently with the maturation of the central nervous system, with both systems sharing key developmental windows. Alterations in the gut microbiota during these periods may impact brain development and increase the risk of psychiatric disorders later in life. Notably, maternal microbiome changes have been shown to influence brain development and contribute to the emergence of psychopathology in offspring.

This study aims to explore the complex and dynamic relationship between gut microbiota and psychiatric disorders, with the goal of advancing our understanding of mental health through the lens of microbiome science.

The Gut-Brain Axis:

The gut-brain axis is a bidirectional communication system that connects the gastrointestinal tract with the central nervous system (CNS) through neural, hormonal, and immune signaling pathways. Among these pathways, the vagus nerve plays a particularly vital role, as it transmits information between the gut and the brain in both directions (10). The gut microbiota can affect this axis through several mechanisms, including the production of neuroactive compounds, modulation of immune responses, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis (11).

The gut microbiome significantly influences both the development and function of the nervous system via its interactions with the gut-brain axis. Some researchers propose the term "microbiome-gut-brain axis" to more accurately reflect the complexity of this system, which involves constant communication between the brain, the gut, and the microbial communities residing in the gastrointestinal tract. This network plays a role in regulating gastrointestinal function, CNS activity, and immune responses simultaneously. The physiological connection between the enteric nervous system (ENS) and the CNS includes several biochemical pathways that coordinate these interactions (12).

This two-way communication system involves the ENS and CNS, with the intestinal microbiota and dietary factors playing a central role in shaping this interaction. Disruptions in this gut-brain communication have been linked to the onset and progression of psychiatric disorders. For instance, a reduction in microbial diversity has been observed in individuals with various mental health conditions and in those with obesity (13).

The gut microbiota is essential for maintaining gastrointestinal health, as it aids in digestion, supports nutrient metabolism, and contributes to the synthesis of essential vitamins. Beyond these functions, the microbiota also has a significant impact on immune function, metabolic regulation, and brain activity, underscoring the importance of the gut-brain axis. This axis facilitates continuous interaction between the central, peripheral, and autonomic nervous systems.

Communication along the gut-brain axis occurs through several pathways: neuronal signals are transmitted via the vagus nerve, hormonal messages are delivered by intestinal peptides, and immune signals are communicated through cytokines. Due to the extensive neural network embedded in the gastrointestinal system, consumed nutrients can activate sensory pathways that relay information about macronutrient content and caloric load to the CNS. The gut microbiota plays a central role in maintaining the stability and proper function of this axis by regulating immune responses and contributing to the broader concept of a gut-brain-immune network. This dynamic interaction is essential for the proper functioning of both the digestive system and the brain, supporting mental and physical well-being.

Gut Microbiota and Psychiatric Disorders:

Depression

Depression is a common psychiatric disorder characterized by persistent feelings of sadness, reduced interest or pleasure in activities, and significant impairment in daily life (13). Numerous studies have identified notable differences in the composition of gut microbiota in individuals with depression compared to those without mental health disorders (15). These alterations often involve a decreased abundance of beneficial bacteria such as Bifidobacterium and Lactobacillus, which are responsible for producing neuroactive substances like gamma-aminobutyric acid (GABA) and serotonin (16).

Animal studies using germ-free mice—mice raised without exposure to any microorganisms—have shown increased depressive-like behaviors. Remarkably, these behaviors were alleviated when gut microbiota from healthy mice were transplanted into the germ-free animals, suggesting a potential causal link between gut microbiota and mood regulation (17). Dietary habits also appear to influence the gut microbiome and its relationship with depression. For example, a large-scale cross-sectional study reported that higher intake of folate and vitamin B12 was inversely associated with the severity of depressive symptoms (18).

Anxiety

Anxiety disorders are characterized by excessive and persistent fear, worry, and behavioral disturbances (19). Like depression, growing evidence suggests that anxiety is also associated with changes in gut microbiota composition.

For instance, administering Lactobacillus rhamnosus to rodents has led to noticeable reductions in anxiety-like behaviors, reinforcing the link between gut bacteria and anxiety (20). Additional clinical observations have noted that individuals with psychiatric conditions such as anxiety, depression, and autism spectrum disorder (ASD) often experience co-occurring gastrointestinal symptoms. These symptoms support the idea of disrupted gut-brain communication playing a role in these conditions (21).

Posttraumatic Stress Disorder (PTSD), once categorized under anxiety disorders, is now classified as a trauma- and stress-related condition. The pathogenesis of anxiety and trauma-related disorders is multifactorial, involving interactions between genetics, epigenetics, and environmental factors. Recent research has increasingly focused on the microbiota-gut-brain (MGB) axis, which plays a key role in understanding the complex biological underpinnings of such psychiatric disorders (22).

Autism Spectrum Disorder (ASD):

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social interaction, communication challenges, and repetitive behaviors. Recent studies have highlighted significant differences in gut microbiota composition between individuals with ASD and neurotypical individuals (23). These differences include a reduction in microbial diversity and an overrepresentation of certain bacterial groups such as Clostridia and Desulfovibrio species.

The human microbiota is crucial for overall health and is increasingly being linked to various neurological and psychiatric disorders. Though the exact mechanisms of the microbiota-gut-brain axis are still being uncovered, it is known that the enteric nervous system (ENS) enables communication between the gut microbiota and the CNS. Under certain conditions, such as in germ-free environments or during antibiotic treatments, the microbiota can influence levels of brain-related chemicals like neurotrophins and monoamine neurotransmitters, which are essential for brain development and function (24).

Schizophrenia

Schizophrenia is a serious mental illness marked by hallucinations, delusions, disorganized thinking, and cognitive decline. Recent studies have revealed that individuals with schizophrenia exhibit notable differences in gut microbiota composition compared to healthy individuals, particularly in bacterial diversity and abundance of specific microbial taxa (25).

The microbiota's genetic potential is vast and influenced by host genetics, medications, diet, and lifestyle changes. Consequently, exploring the gut microbiota may provide valuable insights into the mechanisms of schizophrenia and open pathways for the development of more effective, less invasive treatments with fewer side effects (26).

Production of Neuroactive Metabolites

The gut microbiota has the remarkable capacity to produce a wide range of neuroactive compounds, including critical neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and dopamine, which can significantly influence brain function and behavior (27). Specific strains of bacteria from the Bifidobacterium and Lactobacillus genera are known to synthesize GABA, a key inhibitory neurotransmitter within the central nervous system (CNS) that plays an essential role in regulating anxiety and depressive symptoms (28).

Emerging research has brought attention to dopamine, a neurotransmitter crucial for mood regulation, motivation, and reward pathways in the brain. While it has long been thought to be primarily produced by neurons in the CNS, recent findings reveal that the gut microbiota also plays a role in dopamine production. The term "microbiota-gut-brain axis" is used to describe this relationship. New studies indicate that gut microbes may directly influence dopamine synthesis and release, presenting exciting new directions for research into the gut's role in regulating mental and physical health (29).

Immune System Modulation by Gut Microbiota

In addition to its neurological functions, the gut microbiota also plays a pivotal role in shaping the host's immune responses. An imbalanced immune system has been implicated in various psychiatric and developmental disorders, including depression, autism spectrum disorder (ASD), and schizophrenia. Certain microbial species, such as segmented filamentous bacteria, can activate pro-inflammatory T-helper 17 (Th17) cells, which have been linked to the development of several neuropsychiatric disorders (30).

Alterations in the composition and diversity of the gut microbiota—often caused by antibiotics, diet, or disease—can disrupt immune system regulation and contribute to the onset of immune-related disorders such as inflammatory bowel disease (IBD), allergies, autoimmune conditions, and metabolic syndromes. Gaining a better understanding of the gut-immune connection offers valuable insights into the underlying mechanisms of these disorders and opens the door for microbiota-targeted therapies to restore immune balance and improve health outcomes (31).

The gut microbiota influences the immune system through several key mechanisms. One of the most well-documented pathways involves microbial metabolites, such as short-chain fatty acids (SCFAs)—butyrate, acetate, and propionate—produced during the fermentation of dietary fibers. These SCFAs play critical roles in immune regulation. For example, they promote the development of regulatory T cells, suppress inflammatory cytokine production, and support the integrity of the intestinal epithelial barrier, which is crucial for preventing the entry of pathogens and maintaining immune equilibrium.

Moreover, the microbiota affects the maturation and activation of various immune cells, including T and B lymphocytes. It can also trigger immune signaling pathways that regulate the production of immune molecules and inflammatory mediators. The disruption of this fine-tuned interaction—commonly referred to as dysbiosis—can lead to immune imbalances that are associated with a broad range of diseases.

Regulation of the HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis is a critical neuroendocrine system responsible for regulating the body's response to stress. This axis involves a complex signaling cascade beginning with the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then prompts the adrenal glands to release cortisol, the body's primary stress hormone. Proper functioning of the HPA axis is essential for maintaining emotional, immune, and metabolic balance, and its dysregulation has been closely associated with psychiatric disorders such as anxiety and depression (32).

Emerging research has demonstrated that the gut microbiota plays a regulatory role in modulating the HPA axis. Studies involving germ-free (GF) mice—animals raised in sterile conditions without any exposure to microbes—have shown that these mice exhibit an exaggerated stress response. Specifically, they display elevated levels of CRH, ACTH, and cortisol compared to conventionally raised mice. Interestingly, colonizing these GF mice with microbiota from healthy animals normalizes their stress responses, suggesting that gut microbes are vital for the proper development and regulation of the HPA axis (32).

The gut microbiota influences the HPA axis through multiple mechanisms. These microorganisms can synthesize and secrete bioactive molecules such as neurotransmitters, short-chain fatty acids (SCFAs), and other metabolites. These substances can interact directly or indirectly with components of the neuroendocrine system. In addition, the microbiota can modulate immune cell activity and interact with the enteric nervous system (ENS), establishing a communication bridge between the gut and the brain (33).

This bidirectional relationship between the gut microbiota and the HPA axis is a growing area of research that offers valuable insights into the pathophysiology of stress-related disorders. The disruption of gut microbial composition, or dysbiosis, can negatively impact hormone regulation and stress responses, thereby contributing to the development of mental health conditions such as depression, anxiety, and even metabolic syndromes (34). The findings highlight the gut microbiota's ability to influence not only neurological and immune functions but also endocrine responses critical for stress regulation.

he communication between the gut microbiota and the HPA axis is part of a broader feedback loop that maintains overall physiological homeostasis. The microorganisms residing in the gastrointestinal tract can modulate the secretion of hormones within the HPA axis and influence stress-related behavior. By producing neuroactive compounds such as serotonin, dopamine,

and GABA, the gut microbiota exerts further influence on mood and stress regulation (35). An imbalance in gut microbial communities can disturb this hormonal signaling, potentially leading to heightened stress sensitivity and emotional dysregulation.
Understanding this intricate gut-brain-endocrine connection opens new avenues for the development of microbiota-targeted therapies. These interventions aim to restore balance within the HPA axis and could serve as promising strategies for managing stress-related disorders and enhancing mental and physical health (35).

Probiotics, Prebiotics, and Fecal Microbiota Transplantation (FMT) as Therapeutic Approaches in Psychiatric Disorders

Probiotics are live microorganisms that, when administered in adequate amounts, can provide significant health benefits to the host. A growing body of research supports the positive impact of probiotics on psychiatric symptoms in both preclinical and clinical settings. For instance, a randomized controlled trial conducted by [author/institution] demonstrated that an eight-week supplementation with a probiotic formulation containing Lactobacillus and Bifidobacterium strains significantly reduced depressive symptoms in individuals diagnosed with major depressive disorder, compared to a placebo group. These findings suggest that probiotics may hold therapeutic value in the management of depression and other psychiatric conditions (36). Specific probiotic strains may support mental well-being by modulating the gut-brain axis; however, further investigation is needed to fully understand their mechanisms of action and to determine the most effective formulations for various psychiatric disorders.

Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial gut bacteria. Evidence indicates that prebiotic supplementation can positively alter the gut microbiome, enhance the production of neuroactive substances, and improve psychiatric symptoms. In one study, healthy participants received a galactooligosaccharide-based prebiotic for three weeks. Those who consumed the supplement exhibited significantly lower levels of salivary cortisol, a biomarker for stress, as well as improved emotional processing compared to the placebo group (37). These findings highlight the potential of prebiotics in modulating stress responses and emotional health via the gut-brain axis. However, more research is necessary to understand the mechanisms involved and to explore the role of prebiotics in the treatment of psychiatric conditions.

Fecal Microbiota Transplantation (FMT) involves transferring fecal matter from a healthy donor into the gastrointestinal tract of a recipient, with the aim of restoring microbial balance. While FMT is most used for treating recurrent Clostridium difficile infections, recent studies suggest its potential applications in psychiatry (37).

In human studies, although research remains limited, some findings are encouraging. A small-scale investigation involving 18 children with ASD showed improvements in both behavior and GI symptoms following an eight-week regimen of daily oral microbiota transplantations. Additionally, two case reports noted improved quality of life in adults with inflammatory bowel disease (IBD) and slow transit constipation, though these were measured using subjective scales (37). Despite these positive indications, large-scale, controlled studies are needed to establish the efficacy, safety, and long-term effects of FMT in the treatment of psychiatric disorders.

Conclusion

There is increasing evidence that the gut microbiota plays a crucial role in the development and progression of psychiatric disorders, including depression, anxiety, autism spectrum disorder (ASD), and schizophrenia. The gut-brain axis offers a promising therapeutic target, and interventions such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) have shown potential in improving mental health outcomes. However, further research is essential to fully understand the mechanisms involved and to develop standardized, evidence-based approaches to microbiota-based therapies for psychiatric conditions. Continued exploration in this field is likely to pave the way for more effective and personalized treatments that harness the power of the gut microbiome to support mental well-being.

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