International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 17s, 2025
https://www.theaspd.com/ijes.php

The Gut Microbiome And Mental Health

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ABSTRACT

A balanced gut microbiome is necessary to maintain good mental health.The inexplicable relationship between the gut microbiome and mental health has emerged as a notable area of scientific exploration. Recent research has established a competing bi-directional relationship between the gut microbiome and mental health outcomes.The gut-brain axis(GBA), a bi-directional communication pathway involving the gut microbiome,central nervous system and enteric nervous system,has emerged as a vital element in mental health disorders. GBA can monitor and combine gut activities, connecting emotional and cognitive centers.Communication within the GBA is facilitated by neurology, immunology and endocrinology.This review synthesizes current research on the relationship between gut microbiome and mental health conditions, including depression, anxiety and schizophrenia.This review highlights the key mechanisms of the gut -brain axis, the role of specific microbial species, the impact of diet and lifestyle, dysbiosis in several mental disorders and the therapeutic potential of targeting the microbiome. It also suggests novel avenues for understanding, diagnosing and medicating a wide range of psychiatric conditions. It identifies crucial research gaps, offering insights for advancing mental healthcare through innovative microbiome-informed approaches. This review concludes by illuminating the importance of continued research to further elucidate these complex interactions and translate findings into effective clinical interventions.

Keywords: *Diet, Gut microbiome, Gut microbiota, Mental health, Microbiota-gut-brain-axis, Prebiotics, Probiotics.*

INTRODUCTION

The human gut harbours a vast and diverse community of microorganisms, collectively known as the gut microbiome. The gut microbiome is a complex community of different organisms that live together in a symbiotic state within the human host.(1)This complex ecosystem, comprising bacteria, viruses, fungi, and archaea, plays an important role in several physiological processes, including digestion, nutrient absorption, immune system development, and protection against pathogens.(2) Beyond these well-established functions, an increasing and significant connection exist between the gut microbiome and the central nervous system, a relationship often referred to as the (GBA)gut-brain axis.(3)The microorganisms of the gut microbiome are communicating with the brain through the gut-brain axis.(4)This axis represents a bidirectional communication network that combines neural, endocrine, immune, and metabolic signalling pathways, allowing the gut and the brain to constantly interact and influence each other.(3)The microbiota-gut-brain axis is administered by central nervous system, the enteric nervous system and the autonomous nervous system and by endocrine and neuroimmune pathways.(1)

The rising prevalence of mental health disorders worldwide, including anxiety, depression, schizophrenia, bipolar disorder, and autism spectrum disorder, underscores the urgent need for fruitful prevention and treatment strategies. Emerging research suggests that the gut microbiome may play a critical role in the pathophysiology of these conditions.[2]Diet is an important factor that could alter the gut microbiome,having a role in the development of depression.[1]The composition and function of the gut microbiome are influenced by a millionfactors beyond nutrition, including the mode of birth delivery, aging, presence of diseases, medication intake, sleep patterns, exercise habits, and stress levels.[3] This complexity highlights the need for a thorough understanding of how these factors interact with the gut microbiome and subsequently influence mental health.

Gut microbiota has an adverse impact on our GBA and overall mental health.Chemicals secreted by these bacteria,play an important role in anti-inflammatory responses and help alleviate psychiatric symptoms stemming from inflammation.[5]The identification of changes in the gut microbiome associated with psychological disorders may provide valuable information in the choice of treatment.[5]Given the substantial influence of the gut microbiota on neurodevelopment and neurological health, a balanced gut microbiome is indispensable for favourable brain development and a healthy mental status.[6]The role gut microbiomes play in the control of behaviour, mood,and stress related brain disorders is a relatively young, but fast evolvingresearch field.[7]

This review aims to provide a detailed synthesis of the current literature on the gut-microbe-mental health axis. It will explore the complicate mechanisms of communication along the gut-brain axis, the role of gut microbiomedysbiosis and specific microbial species in the development and progression of various mental health disorders, the significant impact of diet and lifestyle factors, the critical role of microbial metabolites, and the promising therapeutic potential of targeting the gut microbiome for the treatment of mental illness. By examining findings from both International and Indian journals in science and medicine, this review attempts to provide a comprehensive overview of this rapidly evolving and highly significant field of research.

The Gut-Brain Axis: Vehicles of Interaction

The bidirectional communication between the gut and the brain is arbitrated through a complex interplay of several pathways.[3]Recognizing these mechanisms is essential to apprehend how the gut microbiome can influence mental health.

Neural Pathways: The possible impact of the microbiome on Central nervous system signalling is an exponentially growing area of research.[8]The Vagus nerve, tenth cranial nerve and a major component of the autonomic nervous system, plays a significant role in the bidirectional transmission of signals between the brain and the G.I tract.It serves as a primary neural pathway connecting the gut and the brain.[6]Vagus nerve transmits sensory and motor signals throughout the mesenteric organ.[5] Signals influenced by the microbiome and originating from the gut travel along the vagus nerve to the brainstem and other brain regions involved in cognition, mood and behaviour.[9] (Figure-1).Microbial sensory signals convey information about the composition and the activity of the gut microbiota to the brain.[9]Vagus motor efferentsignals from the brain to the G.I tract and other organs.[10]They influence gut motility, secretion of digestive enzymes and modulation of immune responses in Gut associated lymphoid tissue (GALT).[11] For instance, research has demonstrated that the introduction of Campylobacter jejuni in mice led to anxiety - like behaviour through the activation of neuronal regions in the brain via the vagus nerve.[6] The enteric nervous system (ENS), often referred to as the " second brain," is a complex network of neurons within the gastrointestinal tract that can independently regulate gut function but also conveys extensively with the central nervous system.[3] This intricate neural network allows for rapid and direct communication between the gut and the brain.

Endocrine Pathways:A complex network of communication between the brain,the gut and the endocrine system is mentioned as the neuroendocrine pathways of Brain-gut-microbiome system (BGM).Hormones produced in the gut or influenced by the gut microbiome play a significant role in the gut - brain axis.

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The hypothalamic - pituitary - adrenal (HPA) axis, a key regulator of the body's stress response, exhibits bidirectional communication with the gut.[6] (Figure-1).Studies have shown that the gut microbiome can influence the HPA axis's response to stress.[6]Gut hormone involved in energy homeostasis, has also been shown to influence mood andis linked to depression.[12]Notably, the gut microbiome can affect gut hormone levels, featuring another endocrine link between the gut and the brain.[12]

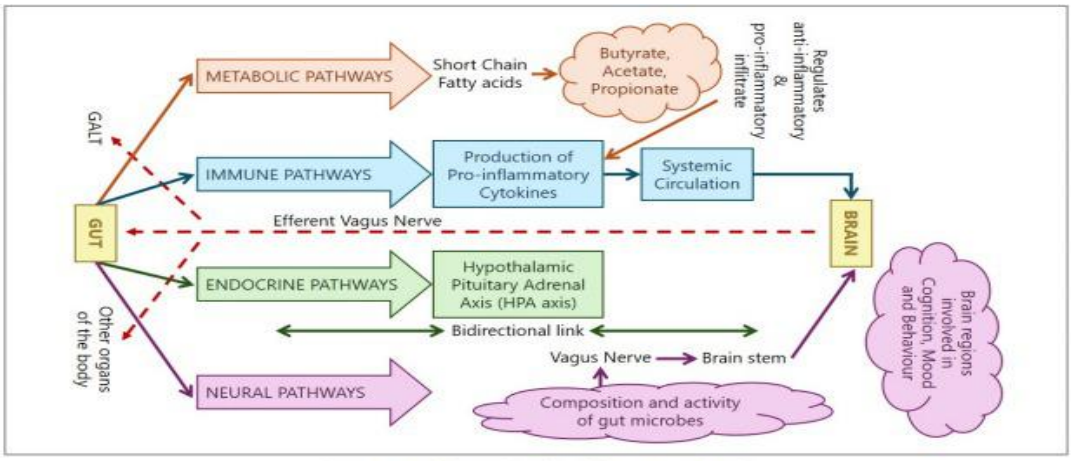

Figure-1: Pathways involved in Gut-Brain Axis

Immune Pathways: The gut microbiome plays a key role in shaping and modulating the host's immune system.[2]Alterations in the gut microbiome can lead to the production of pro-inflammatory cytokines that can enter the systemic circulation and potentially affect brain function.[2](Figure-1).Research has indicated that an environmental contaminant can be included into a molecule produced by the gut bacterium. Morganellamorganii, leads to inflammation and potentially contributing to depression.[13]This finding demonstrates the complex interplay between environmental factors, the gut microbiome, and the immune system in influencing mental health.

Metabolic Pathways: The gut microbiome is a highly metabolically active community, producing a wide array of metabolites, including short - chain fatty acids (SCFAs) such as butyrate, acetate, and propionate.[9] These SCFAs are produced through the fermentation of dietary fibres and have been shown to exert various effects on the brain, including modulating neuroinflammation, influencingthe integrity of the blood - brain barrier, and affecting neurotransmitter activity.[9]Within the gut, short chain fatty acids (SCFAs) regulate anti-inflammatory and proinflammatory cytokines and maintains a supportive environment for commensal bacteria and inhibits pathogen's growth (Figure-1).Gut bacteria can also produce or influence the production of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and dopamine, which play crucial roles in regulating mood and behaviour.[9]Furthermore, other microbial metabolites, such as indoles, have been found to directly regulate brain activity linked to anxiety.[15]Heightened levels of cortisol alter the diversity of the gut microbiota leading to dysbiosis and neuronal damage.[14]They can affect brain function and increases fear response and decreases functional memory. Serotonin concentration within the brain can contribute to the development and progression of depression and anxiety.[16]Histamine has been linked with visceral gut hypersensitivity and studies have linked depression to these elevatedeosinophilic conditions.[17]

Barrier Function: The integrity of the gut barrier and the blood -brain barrier (BBB) is crucial for regulating the communication along the gut-brain axis.[3]Change of the overall gut microbiota diversity leads to a condition known as dysbiosis. It is important to note that dysbiosis can lead to dysregulated immune response that can contribute to chronic inflammation and wide range of negative health implications.The gut barrier, composed of epithelial cells and a mucus layer, selectively allows the passage of substances from the gut lumen into the bloodstream. Dysbiosis can compromise the gut barrier, leading to increased permeability, often referred to as "leaky gut," which allows microbial products and inflammatory molecules to enterthe circulation and potentially affect the brain.[3]Similarly, the BBB,

which protects the brain from harmful substances in the blood, can be influenced by the gut microbiota.[18] Research suggests that SCFAs, produced by gut bacteria, may play a role in managing the development and maintenance of the BBB through epigenetic modifications.[18]

Gut MicrobiomeDysbiosisand its collaboration with Mental Health Disorders

Dysbiosis, characterized by an imbalance in the composition and function of the gut microbiome, has been increasingly interwind in the pathogenesis of various mental health disorders.[2]

Molecular pathogenesis behind Gut-Brain axis (Figure-2). [47,48,49]

The gut microbiota contributes to blood-brain barrier disruption and the molecular pathogenesis of neurodegenerative diseases. A better understanding of the changes happening in the intestinal mucosa in healthy and leaky gut during gut dysbiosis and the impact on immunological responses leading to autoimmune diseases and pathogenesis is the need of the hour. (Figure -2). [47,48,49]

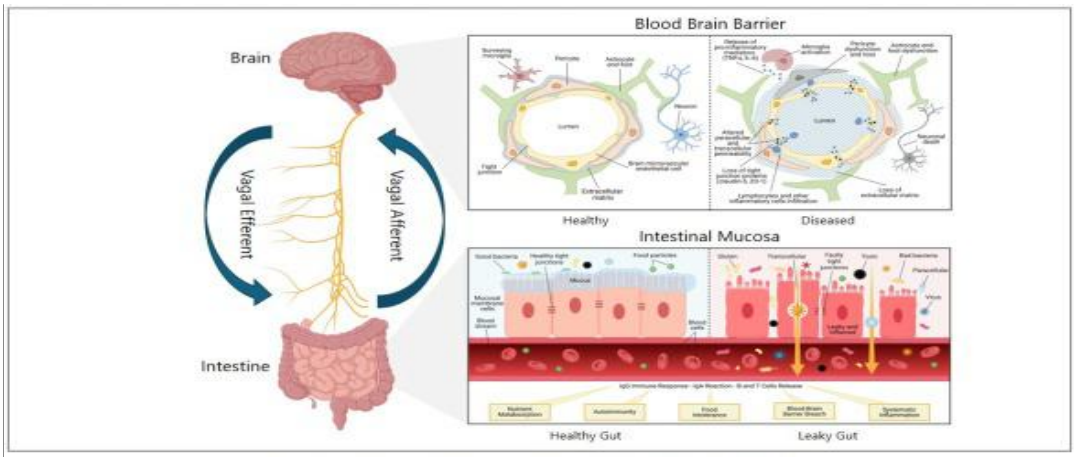

Figure-2: Molecular Pathogenesis behind Gut Brain Axis

Anxiety Disorders: Anxiety is considered as the most common mental disorder.[19]A significant body of research indicates a strong association between alterations in the gut microbiome and anxiety disorders.[20]It is indicated that certain gut microbiotais correlated with anxiety.[21]Studies have reported decreased microbial diversity and abundance in individuals with generalized anxietydisorder (GAD).[22] Specific bacterial genera, such as Eubacterium and Coprococcus, may be associated with a reduced risk of anxiety, while others, like Paraprevotella, Euryarchaeota, Caldivirga, Porphyromonadaceae, and Desulfovibrionales, have been found to be more numerous in individuals with anxiety disorders.[22]Research from Indian journals also supports the link between gut dysbiosis and anxiety, noting that strains like Lactobacillus were less common in individuals with anxiety.[7]Several gut microbiotas such as Prevotella, Lactobacillales, Sellimonas, Streptococcus and Enterococcus were positively correlated with anxiety, while some gut microbiota genera were inversely correlated with anxiety.[21]These consistent findings across various studies suggest a potential role for the gut microbiome in the development and manifestation of anxiety disorders.

Depressive Disorders: The relationship between the gut microbiome and depression has been extensively investigated.[2]Studies have shown that gut microbiomedysbiosis was associated with the occurrence and development of depression.[23,24]While specific bacterial taxa associated with depression can vary between studies, a common theme is the presence of dysbiosis, often depicted by reducedmicrobial diversity and alterations in the abundance of certain genera.[25] For instance, some studies have reported increased levels of Anaerostipes and Blautia, and decreased levels of Bifidobacterium and Faecalibacterium in individuals with major depressive disorder (MDD).[25]The evidence showed that MDD patients had higher levels of Prevotella, Klebsiella, Streptococcus and ClostridiumXI, but lower levels of Bacteroides.[26]Research from Indian journals also highlights this link, suggesting that probiotics and dietary changes may be potential therapeutic strategies for managing depression by fostering a healthy gut microbiome.[27] Some researchers propose that focusing on the functional roles of gut microbes, such as

their ability to produce specific metabolites, might provide a more consistent understanding of their implications in depression.[25]Gut microbiotadysbiosis might be a crucial factor in the pathogenesis of depression via influencing the protein expression in tissues related to the gut brain axis.[21]

Schizophrenia: Emerging evidence suggests a connection between the gut microbiome and schizophrenia.[2]A case control study showed that gut microbiomedysbiosis was found in schizophrenia patients.[28]Metagenomic analysis have identified unique microbial signatures in patients with schizophrenia, with variations observed based on illness status and the type of antipsychotic medication used.[29]Individuals with schizophrenia are highly susceptible to diseases associated with aging like inflammation and Atherosclerosis. Lachnospiraceae is a transdiagnostic marker of psychiatric disease. Lachnospiraceae found in the gut has been associated with anti-inflammatory effects. This species has been found to be depleted in schizophrenia and positively correlated with psychosis symptom disorder.[30]Patients with schizophrenia have shown decreased microbial richness compared to healthy controls, and distinct microbiome variations have been linked to treatment resistance. Research from Indian journals has also explored this link, with one study focusing on the oral microbiome and treatment resistance in schizophrenia.[31]The observation that medication can influence the gut microbiome in schizophrenia highlights the complexity ofstudying this relationship.Several facultative anaerobes, which were rare in healthy individuals were found in schizophrenic patients, such as Lactobacillus fermentum and Enterococcus faceium.[21] Some gut microbiotas were positively correlated to the severity of schizophrenia, such as Lachnospiraceae, Veillonella, Collinsella, Lactobacillus, Succinivibrio, Corynebacterium whereas some were negatively correlated with schizophrenia such as Coprococcus, Ruminococcus, Roseburia, Faecalibacterium.[21]

Bipolar Disorder: Bipolar disorder is a chronic illness that often reoccurs, leading to cognitive and functional impairment.[32]Bipolar disorder patients had areduction in gut microbiota diversity with more Clostridiaceae and Collinsella.[33] It was also reported that bipolar disorder patients had more Actinobacter and Coriobacteria, but less Ruminococcaceae and Faecalibacterium.[34]Alterations in the gut microbiome have also been interrelated withbipolar disorder[2]. Studies suggest that gut microbial dysbiosis may contribute to the progression of bipolar disorder and associated cognitive impairment, potentially through increased intestinalpermeability and altered expression of neurotransmitter receptors.[35] Research from Indian journals indicates a reposition in theFirmicutes/Bacteroidetes ratio in individuals with bipolar disorder.[36]Furthermore, faecal microbiota transplantation (FMT) has shown favourable results in managing bipolar disorder in some studies.[37]

Autism Spectrum Disorder (ASD): A growing body of evidence links gut microbial dysbiosis to autism spectrum disorder (ASD).[2]ASD is a diversified neurodevelopmental disorder.[38]Individuals with ASD often exhibit increased levels of potentially harmful microbes and a reduction in beneficial ones.[39]Several species of gut microbiota were only found in ASD patients, such as Clostridium difficile and Clostridium clostridiioforme.[21] The bacterial strains were positively linked to the levels of 3-hydroxy butyric acid and melatonin but negatively correlated with the level of serotonin.[40]For instance, bounty of Clostridium bacteria has been linked to repetitive behaviour and gastrointestinal problems in ASD.[39] Research from Indian journals also supports this association, highlighting the variations in gut microbiome composition in individuals with ASD and their connection to behavioural symptoms and gastrointestinal issues.[41] These findings suggest that targeting the gut microbiome may be a prospective therapeutic approach for ASD.

Changes in the gut microbiota with each of these disorders are listed in the table below.[5]

Table: Changes in gut microbiota interrelated with mental health disorders[5]

Disorder	Species (Increased Abundance)	Species (Decreased Abundance)
Anxiety/	Alistipes[5]	Bacteroides[5]

Depression	Oscillibacter[5] Clostridium [5] Roseburia[5]	Prevotella[5] Ruminococcus[5] Bifidobacterium[5] Lactobacillus [5] Coprococcus[5] Dialister[5]
Schizophrenia	Anaerococcus[5] Firmicutes[5] Actinobacteria[5] Fusobacteria[5] Acidobacteria[5] Staphylococcus [5] Megasphaera[5] Proteobacteria[5] Succinivibrio[5] Collinsella[5] Clostridium [5] Klebsiella[5] Lactobacillus gasseri[5]	Haemophilus[5] Sutterella[5] Blautia[5] Coprococcus[5] Roseburia[5] Bacteroides[5] Acinetobacteria[5]
Bipolar Disorder	Flavonifractor[5] Actinobacteria[5] Coriobacteriaceae[5]	Faecalibacterium[5] Ruminococcaceae[5] Bifidobacterium[5]
Autism Spectrum Disorder	Clostridium [5] Bacteroides[5] Actinobacterium[5] Proteobacteria[5] Clostridium defense[5] Clostridium orbiscindens[5] Clostridium hathewayi[5] Roseburia[5]	Firmicutes[5] Faecalibacterium[5] Ruminococcus[5]
OCD-obsessive compulsive disorder	Systemic inflammation markers [5]	Oscillospira[5] Odoribacter[5] Anaerostipes[5]

The Effect of Diet and Lifestyle on the Gut Microbiome and Mental Well-being

Diet and lifestyle factors have a mystical impact on the composition and function of the gut microbiome, which in turn can significantly influence mental well-being.[3] Diets rich in fiber and healthy fats, such as the Mediterranean diet, assist a diverse and healthy gut microbiome and are associated with a diminished risk of depression[27]. Conversely, diets high in processed foods and saturated fats, often referred to as the Western diet, can unfavorably impact gut health and aggravate depressive symptoms.[42]Specific dietary components, including fiber, fats, proteins, vitamins, minerals, and polyphenols, play a pivotal role in shaping the gut microbial population.[3]For example, the Mediterranean diet, with its abundance of fruits, vegetables, whole grains, and olive oil, has been steadily linked to improved mental health outcomes.[27]

Prebiotic s and probiotic s are dietary interventions that can modulate the gut microbiome and have shown promise in enhancing mental health.[6] Probiotics, which are live microorganisms, particularly

strains of Lactobacillus and Bifidobacterium, have demonstrated a significant reduction in symptoms of depression and a moderate reduction in anxiety in meta-analyses.[43] An increasing number of studies have disclosed that probiotics particularly the genus Lactobacillus, could prevent and manage several mental disorders by modulating the gut microbiota.[21]Probiotics such as Lactobacillus and Bifidobacterium showed remarkable preventive and therapeutic effects on several mental disorders such as anxiety and depression.[21] Prebiotics, which are non-digestible food components that encourage the growth of beneficial gut bacteria, may have a positive effect on stress and could be favorable for major depressive disorder.[27]Prebiotics exerted shielding effects on mental health.[21] Research from Indian journals also supports the use of both prebiotics and probiotics as novel approaches to promote gut health and regulate mood disorders.[27] Stress, a common aspect of modern life, can also remarkably influence the gut microbiome and mental health.[2] Stress hormones can rapidly alter the levels of certain bacteria in the gut, governing gut dysbiosis.[9]This imbalance can influence the body's stress response, potentially developing a feedback loop that negatively affects mental well-being.[44] Studies have shown that chronic stress can destroy the gut-brain axis at multiple levels, influencing visceral perception and emotional responses.[34]

Microbial Metabolites as Key Facilitators in the Gut-Brain Axis

Microbial metabolites play an important role in mediating the communication between the gut microbiome and the brain. Short-chain fatty acids (SCFAs)produced by the fermentation of dietary fibers by gut bacteria, are predominant metabolites that can influence brain health.[9]Butyrate, acetate, and propionate, the main types of SCFAs, have been shown to have anti-inflammatory effects in the brain, supporting the integrity of the blood-brain barrier, and co-operate in neurotransmitter activity.Gut microbes can also produce or affect the production of various neurotransmitters that are crucial for brain function and mental health. Serotonin, GABA, and dopamine are among the neurotransmitters that can be regulated by the gut microbiome, emphasizing a direct biochemical link between the gut and the brain.[9]Furthermore, other microbial metabolites, such as indoles, have been recognized as having specific effects on brain function, with research showing that they can directly manage anxiety levels. [15] The altered production of these key metabolites in states of dysbiosis may support the observed interrelations between gut microbiome imbalances and various mental disorders.

Curative Powers of Targeting the Gut Microbiome for Mental Health

The growing awareness of the gut-brain axis and the role of the gut microbiome in mental health has opened up new avenues for therapeutic interference.[6]Strategies aimed at modulating the gut microbiome are being analyzed for the treatment of various mental health disorders.

Probiotics, prebiotics, synbiotics and postbiotics:

Probiotics, prebiotics, synbiotics (combinations of probiotics and prebiotics), and postbiotics (bioactive compounds produced by probiotics) are among the various therapeutic approaches being explored.[6]Clinical trials and meta-analyses have shown that probiotic supplementation can greatly reduce symptoms of depression and anxiety.[43]Prebiotics have also established potential benefits for stress and depressive symptoms.[27]

Fecal microbiota transplantation:

Fecal microbiota transplantation (FMT), which involves transferring fecal material from a healthy donor to a recipient, is a growing therapeutic approach for psychiatric disorders.[45]Studies have shown that FMT from healthy donors can lead to a reduction in depressive and anxiety-like symptoms.[46] Furthermore, research from Indian journals suggests that FMT shows great assurance in the management of bipolar disorder.[37] Dietary interventions, such as the adoption of a Mediterranean-style diet, are also being recognized as a therapeutic approach for substantial progress of both gut health and mental well-being.[3]Specific dietary components, like increased fiber intake, can advance the growth of beneficial gut bacteria and the formation of beneficial metabolites.

Conclusion and Future Prospects

The research reviewed herein provides substantial evidence for a noteworthy and elaborate relationship between the gut microbiome and mental health. The intricate communication network of the gut-brain axis, involving neural, endocrine, immune, and metabolic pathways, enables the gut microbiome to exert a profound impact on brain function and emotional well-being. Dysbiosis in the gut microbiome has been constantly associated with a range of mental health disorders, including anxiety, depression, schizophrenia, bipolar disorder, and autism spectrum disorder.

Specific gut microbial species and their metabolic products, such as SCFAs and neurotransmitters, appear to play critical roles in these interactions. Furthermore, diet and lifestyle factors, including stress, have a significant effect on the gut microbiome and accordingly on mental health. This growing understanding has paved the way for investigating novel therapeutic approaches targeting the gut microbiome. Probiotics, prebiotics, and fecal microbiota transplantation have shown hopeful results in preclinical and clinical studies for various mental health conditions. Dietary interventions, such as promoting a healthy and diverse diet rich in fiber, are also budding as important strategies for supporting both gut and mental health.

Inspite of these significant advances, several restrictions remain in the current research. The gut microbiome is an immensely complex ecosystem, and individual variability in its composition and function is considerable. Many studies have identified associations, but establishing clear cause and effect between specific microbial changes and mental health disorders requires further investigation. More developmental studies are needed to understand the progressive dynamics of these associations, and causal studies are essential to further interpret the accurate pathways involved.

Future research should focus on large-scale human studies to authenticate existing findings and establish causality. Mechanistic studies employing advanced techniques are needed to understand the complex interactions between specific microbes, their metabolites, and brain function. Exact randomized controlled trials are essential to evaluate the efficacy and safety of microbiome-based arbitrations for various mental health disorders. Personalized approaches to microbiome modulation, tailored to individual gut profiles, hold remarkable promise. Finally, research on the long-term effects of these interventions is critical to ensure their enduring benefits.

In conclusion, the gut microbiome represents a promising demarcation line in our understanding and

treatment of mental health disorders. Continued research in this energetic field has the potential to revolutionize the way we approach the diagnosis, prevention, and management of these paralyzing conditions.

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