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The Gut-brain Axis: How Microbiota Influence Mental Health and Neurological Function

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Abstract

The gut-brain axis (GBA) represents a critical bidirectional communication network linking the gut microbiota with mental and neurological health, necessitating a comprehensive review to consolidate emerging evidence and elucidate its therapeutic potential. Growing research underscores the role of microbial metabolites, neurotransmitter regulation, and immune pathways in influencing conditions such as depression, anxiety, and neurodegenerative diseases, yet gaps remain in translating these findings into clinical applications. This review addresses the need to integrate multidisciplinary insights into the GBA, offering a foundation for future research and interventions targeting gut-brain interactions. The review highlights the pivotal role of gut microbiota in producing neuroactive compounds, such as short-chain fatty acids (SCFAs) and serotonin, which modulate brain function and behavior. It examines dietary influences, including fiber-rich and fermented foods, in shaping microbial diversity and mental health outcomes. Additionally, the mechanisms of neural, endocrine, and immune pathways in gut-brain communication are explored, alongside clinical evidence linking dysbiosis to psychiatric and neurological disorders. Emerging therapeutic strategies, such as psychobiotics, fecal microbiota transplantation, and personalized nutrition, are discussed as promising interventions. The review also synthesizes findings from key studies on dietary patterns, microbial metabolites, and their impact on cognitive and emotional health. By consolidating this evidence, the review provides a holistic understanding of the GBA's role in health and disease. Future research should prioritize longitudinal and interventional studies to establish causal relationships between gut microbiota and brain function. Standardized methodologies for microbiome analysis and larger, diverse cohorts are needed to enhance reproducibility and clinical relevance. Investigations into the efficacy of microbiome-targeted therapies, including combinations of diet, probiotics, and pharmacologic agents, will be critical for advancing treatment paradigms. Ultimately, unraveling the complexities of the GBA may pave the way for innovative, personalized approaches to mental and neurological healthcare.

Keywords: Gut microbiota, Gut-brain axis, Mental health, Microbial metabolites, Neuroinflammation, Psychobiotics

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Introduction

The GBA represents a complex and dynamic communication network between the gastrointestinal (GI) tract and the central nervous system (CNS) [1-3]. This bidirectional signaling system is increasingly recognized for its role in influencing mental health and neurological function. The gut microbiota, a diverse community of microorganisms residing in the GI tract, plays a pivotal role in this interaction, affecting everything from mood and behavior to cognitive processes and neurological disorders [4-6]. The GBA represents a complex bidirectional communication network whereby the gut microbiota influences neurological function and mental health [7-9]. Recent literature underscores the pivotal role of microbial metabolites, neurotransmitter regulation, and dietary components in modulating this axis [10, 11].

Dietary factors, particularly fiber intake, have been linked to cognitive processes through their impact on the microbiota [12-14]. McGuinness et al. [15] highlights that dietary fiber influences brain health by shaping the composition and activity of gut microbiota, which in turn affects cognitive function. Similarly, dietary supplements and natural compounds are recognized for their potential to modulate neurological health, emphasizing diet's importance in neurological disease management [16]. Microbial metabolites such as SCFAs are identified as key mediators within the GBA. Cheng et al. [17] describe SCFAs-producing bacteria as promising psychobiotics capable of exerting neuroprotective effects by modulating neuroinflammation and neuronal function. Kim [18] further elaborates that these metabolites influence cell-to-cell interactions in the CNS, affecting mood, cognition, and behavior by promoting brain cell maturation and suppressing inflammatory signals.

The production of neurotransmitters by gut microbiota is another critical mechanism through which microbiota influences mental health [19-21]. Gurow et al. [22] expands on this by reviewing how microbiota-regulated neurotransmitters directly impact brain function and neurological disorders. The developmental stage of the microbiota also bears significance. Beretta et al. [23] note that the neonatal period is crucial for establishing a healthy microbiota, which has long-term

implications for cognitive development and mental health. This early colonization influences the bidirectional communication within the GBA, affecting future neurological outcomes.

Emerging research explores the molecular interactions between gut microbes and the CNS, including immune modulation and neurochemical signaling. Bakshi et al. [10] describes how microbial metabolites, neurotransmitters, and immune factors collectively contribute to gut-brain communication, offering insights into potential therapeutic strategies for psychiatric and neurological disorders. Abavisani et al. [24] further investigates how microbiota-produced neurotransmitters influence social behaviors, highlighting the microbiota's broader impact on human behavior. The literature converges on the understanding that the gut microbiota, through its metabolic activities and neurochemical production, plays a fundamental role in maintaining neurological health and influencing mental health disorders. The modulation of this GBA via diet, probiotics, and early microbiota development presents promising avenues for therapeutic intervention [10, 11].

Understanding the GBA

The GBA encompasses various pathways, including neural, hormonal, and immune connections, that facilitate communication between the gut and the brain [25-27]. Chemicals released by gut microbiota can significantly influence brain development and function, starting from infancy. For instance, gut microbiota can regulate brain chemistry and influence neuroendocrine systems associated with stress response, anxiety, and memory function [28, 29]. This intricate interplay suggests that the gut microbiota is not merely a passive inhabitant of the GI tract but an active participant in maintaining mental health [30, 31]. Understanding the GBA's mechanisms and therapeutic potential is crucial for developing interventions targeting these health issues.

The enteric nervous system and the autonomic nervous system are key components of the GBA, facilitating communication between the gut and the brain. The vagus nerve is a critical conduit for transmitting signals from the gut to the brain [10, 32]. The gut microbiota, consisting of trillions of microorganisms, produces metabolites, neurotransmitters, and immune modulators that influence brain function and behavior. Dysbiosis, or imbalances in the gut microbiome, is linked to various neurological and psychiatric disorders [7, 33]. The GBA involves immune signaling and the production of hormones and neurotransmitters, such as serotonin, which are crucial for maintaining CNS homeostasis [34, 35].

The GBA also plays a pivotal role in modulating inflammation, which has been implicated in a range of neuropsychiatric conditions, including depression and Alzheimer's disease [36-38]. Gut microbiota-derived metabolites (Table 1), such as SCFAs, can cross the blood-brain barrier and exert anti-inflammatory effects, thereby protecting against neurodegeneration and cognitive decline [39-41]. Additionally, microbial imbalances have been associated with increased intestinal permeability, or 'leaky gut,' which allows pro-inflammatory molecules to enter systemic circulation and potentially trigger neuroinflammation [42, 43]. This highlights the potential for dietary interventions, probiotics, and prebiotics to restore microbial balance and mitigate inflammation-related brain disorders.

Emerging research also underscores GBA's role in early-life brain development, with gut microbiota composition influencing neurodevelopmental outcomes such as autism spectrum disorder and attention-deficit/hyperactivity disorder [44, 45]. Maternal microbiome health during pregnancy and early postnatal microbial colonization are critical for proper neural circuit formation and immune system regulation [46, 47]. Disruptions in this process, such as through antibiotic exposure or cesarean delivery, may alter microbiota composition and increase susceptibility to neurodevelopmental disorders. These findings suggest that targeted microbiome therapies during critical developmental windows could offer preventive or therapeutic benefits, further emphasizing the GBA's far-reaching implications for mental and neurological health.

The Role of Gut Microbiota in Mental Health

Recent studies have highlighted the profound impact of gut microbiota on mental health. Dysbiosis, or an imbalance in gut microbial composition, has been linked to various psychiatric conditions, including anxiety, depression, and autism spectrum disorders [22, 48]. The gut microbiota influences the production of

Table 1: Key microbial metabolites and their effects on brain function.

Metabolite	Producing bacteria	Production pathway	Mechanism of action	Brain impact	Associated disorders	Potential therapies
SCFAs	*Bacteroides*, *Firmicutes*, *Roseburia*	Dietary fiber fermentation	Modulate neuroinflammation, strengthen BBB, regulate microglia	Neuroprotection, improved cognition	Alzheimer's, depression	High-fiber diet, prebiotics
Serotonin (5-HT)	*Enterococcus*, *Escherichia*, *Streptococcus*	Tryptophan metabolism	Precursor for 5-HT synthesis (90% gut-produced)	Mood regulation, sleep, appetite	Depression, anxiety, IBS	Probiotics (e.g., *Lactobacillus*)
GABA	*Lactobacillus*, *Bifidobacterium*	Glutamate decarboxylation	Binds to CNS GABA receptors, inhibits neuronal excitability	Reduced anxiety, improved sleep	Anxiety disorders, epilepsy	GABA-producing probiotics
Tryptophan derivatives	*Clostridium*, *Bacteroides*	Kynurenine/indole pathways	Modulate neuroinflammation, influence 5-HT/ dopamine balance	Mood/cognition	Depression, schizophrenia	Tryptophan-rich diet, Fecal microbiota transplant
Dopamine precursors	*Bacillus*, *Serratia*	Tyrosine metabolism	Indirectly influence dopaminergic reward pathways	Motivation, motor control	Parkinson's, addiction	Tyrosine supplements
Histamine	*Lactobacillus*, *Enterobacteriaceae*	Histidine decarboxylation	H1 to H4 receptor activation in CNS	Arousal, memory	Migraines, ADHD	Low-histamine diet
Lipopolysaccharides	*Proteobacteria*	Gram-negative bacterial cell walls	Trigger neuroinflammation via TLR4	Cognitive impairment	Neurodegeneration, depression	Anti-inflammatory diets

neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA), which are crucial for mood regulation [22]. Furthermore, alterations in gut microbiota composition can lead to changes in behavior and cognitive function, indicating a direct link between gut health and mental well-being [20, 49].

Alterations in the GBA have been implicated in the pathogenesis of diseases like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. Gut dysbiosis may contribute to these conditions by affecting immune responses and neuroinflammation [7, 32]. The GBA is also linked to mental health conditions such as depression and anxiety. The gut microbiota's role in neurotransmitter production and immune modulation is crucial in these disorders [50]. Studies have shown associations between gut health and cognitive performance, particularly in memory and processing speed. Factors such as diet and lifestyle significantly influence gut microbiota composition and, consequently, cognitive health [51].

The gut microbiota's influence on mental health extends to stress resilience and emotional regulation. Chronic stress can disrupt the gut microbiome, leading to a vicious cycle where dysbiosis exacerbates stress-related disorders such as anxiety and depression [52]. Conversely, certain probiotic strains, often referred to as 'psychobiotics,' have shown promise in reducing stress hormone levels and improving mood by modulating the hypothalamic-pituitary-adrenal axis [53, 54]. Animal and human studies suggest that interventions like fecal microbiota transplantation and targeted probiotic supplementation can restore microbial balance and alleviate symptoms of psychiatric disorders, reinforcing the potential of microbiome-based therapies in mental health treatment.

Additionally, the GBA may play a role in the efficacy of traditional psychiatric medications. Emerging evidence suggests that antidepressants and antipsychotics may partially exert their effects by altering gut microbiota composition, which in turn influences neurotransmitter production and immune function [55-57]. This bidirectional relationship raises the possibility of personalized medicine approaches, where microbiome profiling could guide treatment selection for mental health conditions [58]. Future research should explore how dietary modifications, prebiotics, and probiotics can complement existing therapies to enhance outcomes for individuals with neurological and psychiatric disorders. Understanding these mechanisms could revolutionize mental health care by integrating gut microbiome modulation into standard treatment protocols.

Mechanisms of Interaction

The mechanisms through which gut microbiota influence the brain are multifaceted. This GBA involves multiple pathways, including neural, endocrine, immune, and metabolic routes, and is significantly influenced by gut microbiota. Understanding the mechanisms of gut-brain communication is crucial for exploring its role in various neurological and psychiatric disorders, as well as for developing potential therapeutic strategies. They include the production of microbial metabolites, such as SCFAs, which can modulate neuroinflammation and neurotransmitter synthesis [17, 22]. Additionally, the vagus nerve serves as a critical conduit for signals between the gut and the brain, facilitating communication that can affect stress responses and emotional regulation [20, 59]. Immune system pathways also play a significant role, as gut microbiota can modulate immune responses that impact brain function [48, 60].

Microbial metabolites, SCFAs and other microbial metabolites are key players in gut-brain communication. These metabolites can influence the expression of neurotransmitters and inflammatory cytokines, thereby affecting brain function and behavior [61, 62]. The gut microbiota interacts with the immune system, influencing neuroinflammation and the production of cytokines, which can impact CNS function. This interaction is particularly relevant in stress-related and neurodegenerative disorders [63]. Neuroendocrine and vagal pathways, the gut microbiome can modulate the neuroendocrine system and communicate with the brain via the vagus nerve, affecting stress responses and emotional regulation [62, 63]. Neurotransmitter production, gut microbes are involved in the synthesis of neurotransmitters such as serotonin and dopamine, which are crucial for mood regulation and cognitive functions [64].

- Neural pathways: The vagus nerve is a primary neural pathway facilitating communication between the gut and the brain. It transmits signals from the gut to the brain, influencing mood and cognitive functions [35, 63]. Neurotransmitters and neuropeptides synthesized by gut microbiota can affect brain function. For instance, serotonin, a neurotransmitter involved in mood regulation, is largely produced in the gut [35].

- Endocrine and metabolic pathways: Hormones and metabolites produced by gut microbiota can influence the CNS. For example, SCFAs produced by microbial fermentation have been shown to impact brain function and behavior [7, 65]. Omega-3 fatty acids, particularly EPA and DHA, modulate the GBA by influencing neurotransmitter function and reducing inflammation, which is crucial for maintaining cognitive health [66].

- Immune pathways: The gut microbiota plays a pivotal role in modulating the immune system, which in turn affects brain health. Dysbiosis, or imbalance in gut microbiota, can lead to systemic inflammation, impacting neurological health [7, 67]. Cytokines, which are immune signaling molecules, can cross the blood-brain barrier and influence brain function, linking gut health to neuroinflammatory conditions [68].

- Epigenetic and redox signaling: Gut microbiota can induce epigenetic changes that affect gene expression in both the gut and the brain. These changes can influence neurological health and are particularly relevant in conditions like autism spectrum disorder [63]. Redox signaling, involving reactive oxygen species, is another mechanism through which gut microbiota can affect brain function. Reactive oxygen species can act as signaling molecules, influencing immune and inflammatory responses [63].

While the GBA offers promising avenues for therapeutic interventions, challenges remain in fully understanding its mechanisms. The complexity of the interactions and the variability in individual responses necessitate further research. Additionally, the role of diet, lifestyle, and genetic factors in modulating the GBA highlights the need for personalized approaches in treatment strategies. As research progresses, the potential for novel therapies targeting the GBA continues to grow, offering hope for improved management of neurological and psychiatric disorders.

Dietary Influences on the GBA

The foods we consume play a pivotal role in shaping the composition and function of the gut microbiota, which in turn influences brain health and mental well-being (Table 2) [69, 70]. A diet rich in fiber, such as fruits, vegetables, and whole grains, promotes the growth of beneficial bacteria that produce SCFAs like butyrate, acetate, and propionate

Table 2: Dietary interventions and their impact on GBA health.

Intervention	Key components	Target microbiota	Mechanisms	Clinical evidence	Recommended for	Limitations/ Considerations
High-fiber diet	Whole grains, legumes, resistant starch	*Bifidobacterium*, *Roseburia*, *Faecalibacterium*	Increases SCFAs, reduces intestinal permeability	Improved cognition	Depression, mild cognitive impairment	Gradual increase to avoid bloating
Fermented foods	Yogurt, kefir, kimchi, miso	*Lactobacillus*, *Streptococcus*	Enhances GABA, reduces cortisol	Reduced anxiety	Generalized anxiety, stress	Variable microbial content
Omega-3 supplementation	EPA/DHA (fish oil, algae)	*Akkermansia*, *Faecalibacterium*	Anti-inflammatory, supports neuronal membranes	Lower depression scores	MDD, inflammation-related disorders	High doses may interact with blood thinners
Polyphenol-rich foods	Berries, dark chocolate, green tea	*Bifidobacterium*, *Lactobacillus*	Antioxidant inhibits NF-κB	Improved memory	Age-related cognitive decline	Bioavailability varies
Mediterranean diet	Olive oil, nuts, fish, leafy greens	Diverse microbiota enrichment	Combines anti-inflammatory and prebiotic effects	30% lower depression risk	Depression, cardiovascular health	Cultural dietary adaptation needed
Probiotic supplements	*Lactobacillus rhamnosus*, *Bifidobacterium longum*	Strain-specific modulation	Direct neurotransmitter production (e.g., GABA)	Mixed results for anxiety	IBS, stress-related disorders	Strain specificity critical
Fecal microbiota transplant	Donor microbiota	Global microbial restructuring	Restores eubiosis, reduces LPS	Promising for autism	Refractory *Clostridioides difficile*, ASD	Long-term safety unclear
Time-restricted eating	12 to 16 h fasting windows	Promotes *Akkermansia*	Enhances autophagy, reduces oxidative stress	Improved mood	Metabolic syndrome, neurodegeneration	Adherence challenges

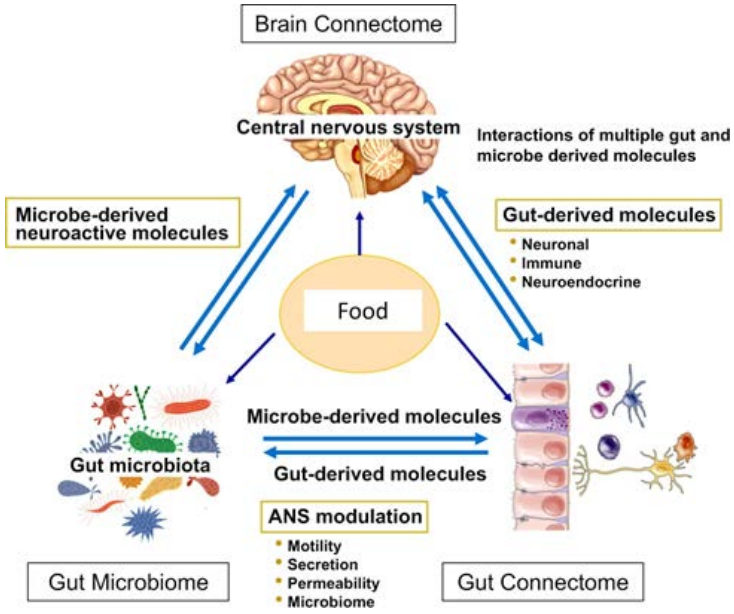

Figure 1: The influence of food on the brain gut microbiome system [73].

[71, 72]. These metabolites have anti-inflammatory effects and support the integrity of the blood-brain barrier, potentially reducing the risk of neurodegenerative and mood disorders. Conversely, a Western diet high in processed foods, sugars, and saturated fats can lead to dysbiosis, increased intestinal permeability, and systemic inflammation, which are linked to depression, anxiety, and cognitive decline (Figure 1) [73].

Fermented foods, such as yogurt, kefir, sauerkraut, and kimchi, are natural sources of probiotics that can enhance microbial diversity and improve gut-brain communication [74]. These foods contain live beneficial bacteria that help restore gut balance and have been associated with reduced symptoms of anxiety and depression. Additionally, polyphenol-rich foods like berries, dark chocolate, green tea, and olive oil act as prebiotics, fueling the growth of beneficial microbes while exerting antioxidants and anti-inflammatory effects that protect brain function [75, 76]. Integrating these foods into daily nutrition may offer a simple yet effective strategy for supporting mental health through the GBA.

The Mediterranean diet, characterized by high intake of plant-based foods, healthy fats, and lean proteins, has been extensively studied for its positive effects on both gut and brain health [77]. Research suggests that adherence to this dietary pattern is associated with a lower risk of depression, Alzheimer's disease, and Parkinson's disease, likely due to its ability to promote a diverse and stable gut microbiome [78, 79]. In contrast, diets high in ultra-processed foods and artificial additives have been linked to increased neuroinflammation and impaired cognitive function, highlighting the importance of whole nutrient-dense foods in maintaining optimal brain-gut interactions.

Emerging evidence also suggests that intermittent fasting and time-restricted eating may benefit the GBA by promoting microbial diversity and enhancing autophagy, a cellular cleanup process that supports neuronal health [80, 81]. These dietary approaches have been shown to reduce oxidative stress, improve mood regulation, and potentially lower the risk of neurodegenerative diseases. However, individual

responses to dietary interventions can vary based on genetic factors, baseline gut microbiota composition, and lifestyle, underscoring the need for personalized nutrition strategies in mental and cognitive health management.

Future research should explore how specific dietary components interact with the gut microbiome to influence brain function, as well as the potential for tailored nutritional interventions in treating psychiatric and neurological disorders. Combining dietary modifications with probiotics, prebiotics, and other gut-targeted therapies could open new avenues for preventing and managing conditions like depression, anxiety, and dementia [82, 83]. As our understanding of the GBA deepens, nutrition may emerge as a cornerstone of mental health care, offering a natural and accessible way to support both gut and brain well-being.

In summary, diet is a significant factor influencing the composition and diversity of gut microbiota. Nutritional strategies, such as the incorporation of probiotics and prebiotics, have shown promise in modulating gut health and, consequently, mental health outcomes [15, 84]. The Mediterranean diet, rich in antioxidants and anti-inflammatory compounds, has been associated with improved cognitive function and reduced risk of neurodegenerative diseases [16]. Furthermore, dietary fiber has emerged as a key player in promoting gut health, with studies suggesting its role in enhancing cognitive function through microbiota-mediated mechanisms [15].

Therapeutic Implications

The understanding of the GBA opens new avenues for therapeutic interventions targeting mental health disorders (Figure 2) [85]. Psychobiotics, which are live microorganisms that confer mental health benefits, are being explored as potential treatments for conditions such as depression and anxiety [17, 22]. Probiotics, prebiotics, and dietary interventions are being explored to modulate the gut microbiota and improve neurological and mental health outcomes. Fecal microbiota transplantation and dietary modifications are also being investigated as strategies to restore gut microbiota balance and improve mental health outcomes [22, 48].

While the GBA offers promising avenues for therapeutic interventions, challenges remain in understanding its complex mechanisms and individual variability. The need for standardized methods to assess gut microbiome composition and function is critical for advancing research in this field [33]. Additionally, the multifactorial nature of the GBA necessitates a holistic approach to treatment, considering both biological and lifestyle factors. As research progresses, the potential for personalized medicine targeting the GBA becomes increasingly apparent, offering hope for more effective management of neurological and mental health disorders.

Clinical Studies

The GBA is a complex communication network linking the GI tract and the CNS, with significant implications for various health conditions. Clinical studies have explored the GBA's role in glucose metabolism, psychiatric disorders, functional GI disorders, and autoimmune diseases. These studies highlight the potential of the GBA as a therapeutic target, though further research is needed to fully understand its mechanisms and effects.

A study by Pendharkar et al. [86] investigated the role of various glucoregulatory peptides in individuals who experienced acute pancreatitis and subsequently developed abnormal glucose metabolism

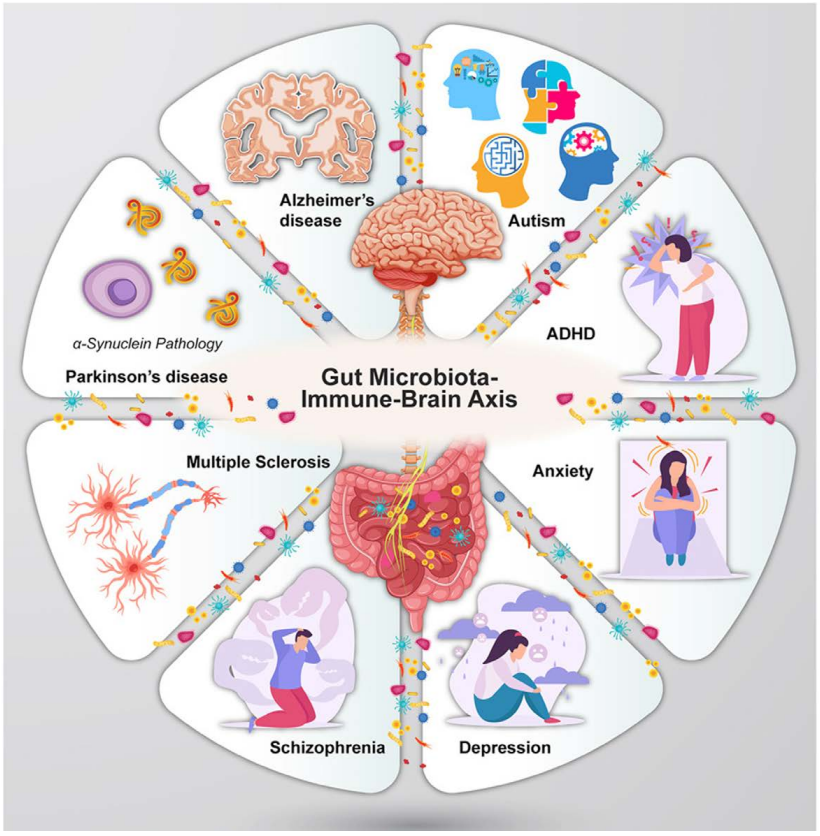

Figure 2: Therapeutic application of GBA [85].

(AGM). A total of 83 individuals were included in the study, out of which 30 (36%) developed AGM after their acute pancreatitis episode. The researchers measured fasting levels of several glucoregulatory peptides, including glucagon-like peptide-1 (GLP-1), glicentin, oxyntomodulin, peptide YY, ghrelin, cholecystokinin, vasoactive intestinal peptide (VIP), and secretin. Among the peptides studied, the highest quartile of oxyntomodulin levels was significantly lower in individuals with AGM compared to the lowest quartile, with a prevalence ratio (PR) of 0.50 (95% confidence interval (CI): 0.21, 1.20; p = 0.005). Similar results were observed for glicentin, with a PR of 0.26 (95% CI: 0.13, 0.54; p < 0.001). The PR for VIP was 0.34 (95% CI: 0.13, 0.89; p = 0.043). Other peptides, including peptide YY, GLP-1, cholecystokinin, ghrelin, and secretin, did not show significant associations with AGM. The study concluded that fasting levels of oxyntomodulin, glicentin, and VIP are significantly decreased in patients with defective glucose homeostasis following acute pancreatitis. Oxyntomodulin, in particular, is highlighted as a promising therapeutic target for future clinical studies focused on diabetes related to exocrine pancreatic diseases. These findings suggest that the GBA plays a crucial role in regulating glucose metabolism after acute pancreatitis, and targeting specific peptides may offer new avenues for treatment [86].

A study by Xu et al. [87] aimed to explore the causal relationships between functional GI disorders and variations in cerebral cortex structures, utilizing Mendelian randomization analyses. A significant negative causal correlation was found between functional dyspepsia and the thickness of the rostral anterior cingulate cortex. The results indicated: $\beta = -0.142$ (95% CI: −0.209 to −0.074, P.FDR = 0.004) and $\beta = -0.112$ (95% CI: −0.163 to −0.006, P.FDR = 0.003). This correlation persisted even after adjusting for multiple variables, with $\beta = -0.137$ (95% CI: −0.187 to −0.087, P.FDR = $1.81 \times 10-5$) and $\beta = -0.109$ (95% CI: −0.158 to −0.06, P.FDR = 0.002). The study also found a positive causal correlation between functional dyspepsia and the globally adjusted thickness of the superior frontal gyrus, with results showing: $\beta = 0.107$ (95% CI: 0.062 to 0.153, P.FDR = 0.001). A significant causal association was identified between the surface area of the caudal anterior cingulate cortex and irritable bowel syndrome, with an odds ratio (OR) of 1.267 (95% CI: 1.128 to 1.424, P.FDR = 0.02). The analysis explored whether anxiety and depression mediated the relationship between functional GI disorders and cerebral cortex structures. However, the findings indicated that neither anxiety nor depression played a mediating role in these relationships. The research provides strong Mendelian randomization evidence of a bidirectional causal relationship between functional GI disorders and cerebral cortex structures, confirming the two-way communication along the GBA. This insight enhances the understanding of the underlying pathophysiology and may guide future therapeutic approaches. These results highlight the complex interactions between brain structures and GI disorders, emphasizing the need for further research in this area [87].

A systematic review by Fairbrass et al. [88] included 12 longitudinal studies with a total of 9,192 patients, focusing on the relationship between anxiety, depression, and inflammatory bowel disease (IBD) outcomes. Brain-to-gut effects: Patients with anxiety symptoms at baseline showed a 68% higher risk of escalation of therapy (relative risk (RR) = 1.68; 95% CI: 1.18 to 2.40). A 72% higher risk of hospitalization (RR = 1.72; 95% CI: 1.01 to 2.95). A 30% higher risk of emergency department attendance (RR = 1.30; 95% CI: 1.21 to 1.39). Increased risk of experiencing any adverse outcome (composite measure). Patients with depression at baseline had: A 60% higher risk of disease flare (RR = 1.60; 95% CI: 1.21 to 2.12), a 41% higher risk of escalation of therapy (RR = 1.41; 95% CI: 1.08 to 1.84), a 35% higher risk of hospitalization (RR = 1.35; 95% CI: 1.17 to 1.57), a 38% higher risk of emergency department attendance (RR = 1.38; 95% CI: 1.22 to 1.56), and a 63% higher risk of requiring surgery (RR = 1.63; 95% CI: 1.19 to 2.22). Gut-to-brain effects: Active IBD at baseline was linked to future development of anxiety or depression. A 124% increased risk of developing anxiety (RR = 2.24; 95% CI: 1.25 to 4.01) and a 49% increased risk of developing depression (RR = 1.49; 95% CI: 1.11 to 1.98). The study concludes that there are significant bidirectional effects between the brain and gut in IBD, influencing both the psychological health of patients and the natural history of the disease. These findings highlight the importance of addressing mental health in the management of IBD to potentially improve patient outcomes [88].

A study Açik et al. [89] investigated the relationship between dietary quality and mental health outcomes in female adults, focusing on two dietary quality indices: Healthy eating index (HEI)-2015 and the Mediterranean diet adherence measured by the prevention with mediterranean diet (PREDIMED). The research included 977 female participants from a social facility in Ankara, Turkey. Dietary intake was assessed using a 24 h dietary recall interview, which helped in developing the HEI-2015 score. The mental health of participants was evaluated using depression, anxiety, and stress scale (DASS)-42, which measures common psychological disorders. Participants with a high PREDIMED score exhibited significantly lower odds of experiencing depression (OR: 0.39, 95% CI: 0.25 to 0.58), anxiety (OR: 0.68, 95% CI: 0.46 to 1.00), and stress (OR: 0.42, 95% CI: 0.28 to 0.65) compared to those with a low PREDIMED score. This indicates a strong inverse relationship between adherence to the Mediterranean diet and mental health disorders. The HEI-2015 showed a weaker association with mental health outcomes compared to the PREDIMED results. Participants with lower HEI-2015 scores continued to exhibit depressive and anxiety symptoms even after full adjustment for confounding factors. The study concluded that there is a significant association between poorer dietary quality and adverse mental health outcomes, particularly highlighting the benefits of adhering to a mediterranean diet as measured by the PREDIMED index. The findings suggest that improving dietary quality may be a potential strategy for enhancing mental health in female adults. These results underscore the importance of dietary patterns in influencing mental health, particularly in women, and suggest that interventions aimed at improving diet quality could be beneficial for mental well-being [89].

A study Nematollahi et al. [90] aimed to explore the relationships between dietary behaviors, mental health, and general health among employees of Isfahan University of Medical Sciences. The study included 4,763 participants and utilized four questionnaires to gather data on demographic characteristics, dietary behaviors, anxiety and depression levels, and general health status. The analysis was conducted using structural equation modeling with 4 unobserved latent variables and 16 observed variables. The regression coefficient for dietary behavior on mental health was -1 (with a standard error of 0.37), which was statistically significant (p = 0.007). This suggests that poorer dietary behaviors are associated with worse mental health outcomes. The regression coefficient for mental health on general health (GHQ) was 0.02 (with a standard error of 0.01), also statistically significant (p = 0.01). This indicates that worse mental health is linked to poorer general health status. The estimated root mean square error of approximation was 0.062, with a 90% CI of 0.060 to 0.065. The comparative fit indices were both 0.866 for the incremental fit index and the comparative fit indices itself, indicating that the model adequately represents the data. The findings suggest a clear pathway where lower dietary behavior

scores correlate with higher mental health problems, and higher scores in depression and/or anxiety are associated with poorer general health outcomes. This emphasizes the importance of dietary behaviors in influencing mental health and overall health status. In summary, the study highlights the significant mediating role of mental health in the relationship between dietary behaviors and general health, suggesting that improving dietary habits could potentially enhance mental health and, consequently, general health [90].

A study by Fayyazi et al. [91] explored the relationship between dietary patterns and mental health issues among college students, focusing on depression, anxiety, and stress. The research involved 412 college students from Iran, who were assessed for their dietary intake and mental health status using specific questionnaires. Dietary intake was evaluated through a 168-item semi-quantitative food frequency questionnaire, while mental health was measured using a 42-item DASS. The study identified major dietary patterns using principal component analysis. Two primary patterns were highlighted: the 'plant-based' dietary pattern and the 'Western' dietary pattern. Students in the third tertile of the 'plant-based' dietary pattern had significantly lower odds of experiencing depression compared to those in the first tertile. The OR was 0.44 (95% CI: 0.17 to 0.65, $p < 0.01$) in model I and 0.42 (95% CI: 0.17 to 0.67, $p < 0.01$) in model II. This indicates a strong inverse association between the 'plant-based' diet and depression. The 'plant-based' dietary pattern did not show a significant association with stress. However, there was a marginally significant association with anxiety in model II, where the OR was 0.53 (95% CI: 0.36 to 0.98, $p = 0.07$). The 'Western' dietary pattern was not associated with the likelihood of depression, stress, or anxiety, indicating that it may not have a protective effect on mental health among the students studied. The study concluded that a strong inverse relationship exists between the 'plant-based' dietary pattern and depression among college students. In contrast, the 'Western' dietary pattern did not correlate with mental health issues, suggesting the potential benefits of a plant-based diet for mental well-being. These results highlight the importance of dietary choices in relation to mental health, particularly in young adults. Further research is encouraged to explore these associations in more depth [91].

A paper by Montgomery et al. [92] presents a systematic review and meta-analyses investigating the effects of specific nutrients and dietary patterns on mental health outcomes, particularly focusing on depression and anxiety in adults. A total of 68 studies were included in the review. Out of these, 5 studies focused on dietary patterns, while 63 studies examined nutrient interventions. The nutrients studied included omega-3 fatty acids (22 studies), vitamin D (18 studies), B-vitamins (10 studies), zinc (7 studies), iron (1 study), vitamin D combined with calcium (4 studies), and omega-3 combined with vitamin D (1 study). The meta-analysis revealed that zinc supplementation significantly reduced depression scores. The standardized mean difference (SMD) in depression scores was −0.67, with a 95% CI: of −0.96 to −0.37. This finding was based on 4 studies and was rated with moderate certainty using the GRADE framework. The analysis showed no significant effects of omega-3 fatty acids on depression, with a SMD of 0.26 (95% CI: −0.64 to 0.12) based on 10 studies, also rated with moderate certainty. Vitamin D: Similar to omega-3, vitamin D did not show significant effects on depression, with a SMD of 0.07 (95% CI: 0.34 to 0.47) from 10 studies, rated with moderate certainty. The mediterranean diet was also assessed, but no significant effects on depression were found, with a SMD of −0.95 (95% CI: −1.90 to 0.01) based on 3 studies, rated with high certainty. B-vitamins and dietary approaches to stop hypertension diet: There were insufficient studies available to conduct a meta-analysis for B-vitamins in relation to depression. Additionally, there were not enough studies to analyze the dietary approaches to stop hypertension diet. The results indicate that zinc supplementation has beneficial effects on reducing depression, while omega-3 fatty acids, vitamin D, and the mediterranean diet did not show significant effects. The authors emphasize the need for further intervention trials to better understand the impact of specific nutritional factors on mental health [92].

An umbrella review by Xu et al. [93] identified a total of 28 meta-analyses that provided 40 summary estimates regarding the relationship between dietary factors and depression. These studies focused on various dietary patterns, food groups, and nutrients. There was moderate quality evidence supporting the idea that a healthy diet, adherence to the alternate HEI, consumption of fish, coffee, and light to moderate alcohol intake (less than 40 grams per day) were associated with a lower risk of depression. Specifically, the RR for these associations were: with healthy diet (RR: 0.74, 95% CI: 0.48 to 0.99, I2 = 89.8%), fish (RR: 0.88, 95% CI: 0.79 to 0.97, I2 = 0.0%), coffee (RR: 0.89, 95% CI: 0.84 to 0.94, I2 = 32.9%), dietary zinc (RR: 0.66, 95% CI: 0.50 to 0.82, I2 = 13.9%), light to moderate alcohol (<40 g/day, RR: 0.77, 95% CI: 0.74 to 0.83, I2 = 20.5%), as well as for positive association with sugar-sweetened beverages (RR: 1.05, 95% CI: 1.01 to 1.09, I2 = 0.0%). For depression treatment, moderate-quality evidence was identified for the effects of probiotic (standardized mean difference: −0.31, 95% CI: −0.56 to −0.07, I2 = 48.2%), omega-3 polyunsaturated fatty acid (SMD: −0.28, 95% CI: −0.47 to −0.09, I2 = 75.0%) and acetyl-L-carnitine (SMD: −1.10, 95% CI: −1.65 to −0.56, I2 = 86.0%) supplementations. Overall quality of evidence remains low or very low for most associations, indicating a need for further research to clarify these relationships [93].

While the evidence supports the role of diet in mental health, it is important to consider the limitations and variability in study designs. Many studies are cross-sectional, which limits the ability to infer causality. Additionally, the quality of evidence varies, with some studies having low methodological quality. The complexity of diet and its interaction with other lifestyle factors also complicates the interpretation of results. Therefore, while dietary interventions hold promise, further well-designed prospective studies are needed to establish stronger causal links and to explore the mechanisms by which diet influences mental health. This would help in formulating more effective dietary guidelines and interventions for mental health improvement.

Conclusion

The exploration of the GBA underscores its critical role in bridging GI health with mental and neurological well-being. The intricate bidirectional communication between gut microbiota and the CNS, mediated by microbial metabolites, neurotransmitter production, and immune pathways, highlights the profound impact of gut health on conditions such as depression, anxiety, and neurodegenerative diseases. Dietary interventions, including fiber-rich foods, probiotics, and the Mediterranean diet, have emerged as powerful tools to modulate the gut microbiome, offering promising avenues for enhancing cognitive function and emotional resilience. This growing body of evidence emphasizes the importance of maintaining a balanced gut microbiota as a cornerstone of both physical and mental health.

Looking ahead, the GBA presents a transformative opportunity for advancing personalized medicine and therapeutic strategies. While challenges remain in fully deciphering complex mechanisms, the

potential for microbiome-based interventions-such as psychobiotics, fecal microbiota transplantation, and targeted dietary plans-is immense. Future research should focus on elucidating causal relationships, standardizing methodologies, and integrating GBA modulation into clinical practice. By deepening our understanding of the GBA, we can unlock innovative approaches to prevent and treat mental health disorders, ultimately improving quality of life for individuals worldwide. The GBA is not just a scientific curiosity but a pivotal frontier in the quest for holistic health.

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Conflict of Interest

None.

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