A Central Regulator of Obesity & Cognitive Function

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***Abstract*—The gut microbiota and the central nervous system are connected by the microbiota-gut-brain axis (MGBA). This complex bidirectional communication network has a major impact on mental health, cognitive function, and metabolic control. The gut microbiota, which comprises billions of microorganisms, mediates vital functions like hunger regulation, neuroinflammation, and neurogenesis by interacting with host physiological systems through neurological, hormonal, and immunological pathways. Numerous neurodevelopmental, psychiatric, and neurodegenerative conditions, such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, Alzheimer's disease, and obesity, have been linked to dysbiosis, an imbalance in the makeup of gut microbes. The mechanics behind the MGBA are explained in this review, with a focus on how it affects cognitive function and exercise motivation. To improve mental health and gut health, we also look into therapeutic implications, such as microbial-based therapies, dietary adjustments, and lifestyle changes. By synthesising previous research, we demonstrate how targeting the MGBA may be a novel strategy for managing and preventing neuropsychiatric illnesses and related metabolic diseases. This could open the door for creative approaches to enhance general health and quality of life.**

***Index Terms*—Microbiota, Neuropsychiatric disorders, Cognitive function, Dysbiosis, Metabolic health, Obesity**

1. INTRODUCTION

It has long been known that the stomach and brain have a complex relationship, and new study has shown how important gut microbiota is to this link. The gut microbiota, which is made up of trillions of microorganisms, interacts with the physiological systems of the host and affects neurobiological activities via a variety of routes, such as immune responses, neuronal signalling, and metabolic processes (Hou et al., 2022; Mitrea et al., 2022). The effects of the microbiota-gut-brain axis (MGBA) on metabolic health, exercise motivation, neuropsychiatric diseases, and cognitive performance. The gut microbiota and the CNS are connected by a bidirectional communication network known as the MGBA. This intricate system is essential for controlling cognitive function and metabolic health in addition to having an impact on mental health and neurodevelopment. (Carabotti et al., 2015; Y.-K. Kim & Shin, 2018; Nakhal et al., 2024a).

The gut microbiome is made up of trillions of microorganisms that live in the human gut, including bacteria, viruses, fungus, and archaea. These microbes carry out vital tasks such immune response modulation, vitamin synthesis, and complicated carbohydrate digestion. In addition to their metabolic functions, gut microbiota can affect brain function via a number of routes, such as immunological, hormonal, and neurological. Short-chain fatty acids (SCFAs) are one example of a microbial metabolite that can penetrate the blood-brain barrier and have neuroprotective effects by encouraging neurogenesis and lowering neuroinflammation (Shreiner et al., 2015; Thursby & Juge, 2017).

A number of neurodevelopmental, neurodegenerative, and psychiatric illnesses are linked to dysbiosis, or changes in the variety and composition of the gut microbiota. Unbalances in gut microbiota have been connected to neurodegenerative disorders including Alzheimer's and Parkinson's disease, as well as conditions like autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression (Bicknell et al., 2023; Cenit et al., 2017). Given the significance of the MGBA for mental health and cognitive function, therapeutic strategies that focus on the gut microbiota may provide new ways to prevent or cure these disorders. Apart from its effects on mental health, the MGBA is essential for controlling behavior and physical health (Ashique et al., 2024; Toader et al., 2024). According to studies, the gut microbiota affects the neurochemical pathways linked to reward and pleasure, which in turn affects desire for physical activity and exercise. For example, during exercise, gut-derived signals can increase dopamine release in the brain, indicating that the microbiome may contribute to encouraging an active lifestyle (W. Sun et al., 2023). Furthermore, the gut microbiota affects energy balance, hunger management, and fat metabolism, making the MGBA essential to metabolic regulation (Han et al., 2021; Pizarroso et al., 2021). Obesity and metabolic disorders have been associated with dysbiosis, suggesting that treatments that target the gut microbiota may be useful in treating these conditions. (C. D. Davis, 2016; (Cryan et al., 2019; Mitra et al., 2023; Nakhal et al., 2024b).

2. MECHANISMS OF THE MICROBIOTA-GUT-BRAIN AXIS

2.1. Communication Pathways

The enteric nervous system (ENS), often referred to as the "second brain," comprises a complex network of neurons embedded within the gut wall. This system is capable of independent function but also communicates extensively with the central nervous system via the vagus nerve (Fleming et al., 2020; Rao & Gershon, 2018). The vagus nerve carries signals bidirectionally, conveying information about gut distension, nutrient content, and inflammation to the brain. This neural communication plays a vital role in regulating emotional states, appetite, and stress responses, highlighting the ENS's integral role in the MGBA (Breit et al., 2018; Yu et al., 2020).

The gut microbiota influences the production and secretion of various hormones that regulate metabolism, appetite, and mood. For instance, glucagon-like peptide-1 (GLP-1), released from intestinal L cells, enhances insulin secretion and reduces appetite. The interplay between gut hormones and brain centers that regulate hunger and satiety can impact both emotional and cognitive functions. Dysregulation of these hormones due to microbiota imbalances may lead to metabolic disorders and affect mood regulation (Lupien-Meilleur et al., 2020; L.-J. Sun et al., 2020; van Son et al., 2021).

The gut microbiota plays a crucial role in shaping the host's immune responses. It influences the maturation of immune cells and the production of cytokines, which can impact neuroinflammation and brain health. For example, pro-inflammatory cytokines released during gut dysbiosis can contribute to neuroinflammatory processes implicated in various neuropsychiatric disorders, including depression and anxiety. Additionally, the microbiota helps maintain the integrity of the blood-brain barrier, further emphasizing its role in immune regulation (Salvo-Romero et al., 2020; Sittipo et al., 2022; Wu & Wu, 2012; Zhao et al., 2023).

2.2. Microbial Metabolites and their Effect

Byproducts of microbial metabolism, microbial metabolites have the ability to affect behavior and brain health. Gut bacteria ferment dietary fibers to create SCFAs, including butyrate, propionate, and acetate. It has been demonstrated that these SCFAs can penetrate the blood-brain barrier and have neuroprotective effects through lowering neuroinflammation, increasing neurogenesis, and modifying neurotransmitter levels. For instance, higher levels of brain-derived neurotrophic factor (BDNF), which is essential for memory, learning, and synaptic plasticity, have been linked to butyrate (Fusco et al., 2023; O'Riordan et al., 2022; Silva et al., 2020). Other microbial metabolites, such as branched-chain amino acids and tryptophan derivatives, can influence neurotransmitter synthesis, further linking the gut microbiota to cognitive and emotional functions (C.-S. Kim, 2024; Liu et al., 2022; Rusch et al., 2023).

3. FACTORS INFLUENCING MICROBIOTA COMPOSITION

3.1. Early Life Influences

The mode of delivery can significantly impact the initial colonization of the gut microbiota. Infants born via cesarean section are often exposed to fewer maternal bacteria, which can result in a less diverse microbiota (Korpela, 2021). This reduced diversity has been linked to an increased risk of developing neurodevelopmental disorders, such as ASD. The early establishment of a healthy microbiome is crucial for optimal brain development and function (Lai et al., 2024; Mitchell et al., 2020; Zhang et al., 2021).

The early nutritional milieu, which includes breastfeeding and the introduction of solid meals, is crucial in determining the composition of the gut microbiota (Catassi et al., 2024). Breastfeeding supplies vital nutrients and immunoglobulins that maintain gut health, as well as encouraging the growth of good bacteria. On the other hand, a diet heavy in processed foods and low in fiber can cause dysbiosis, which can have detrimental effects on both physical and mental health (Boudry et al., 2021; E. C. Davis et al., 2022; Laursen, 2021).

3.2. Aging and Lifestyle

The composition and diversity of gut microbiota tend to decrease with aging. Increased systemic inflammation and cognitive loss are linked to this decrease in microbial diversity, and these two conditions are risk factors for neurodegenerative disorders. Age-related cognitive deficits may worsen in older persons due to changing microbiome profiles that may impact gut-brain communication pathways (Molinero et al., 2023). Stressors from the environment and psychology can cause major alterations in the makeup of the gut microbiota. Dysbiosis is the result of chronic stress, which has been demonstrated to reduce helpful bacteria and increase the number of harmful germs. A vicious cycle of stress and declining gut health can result from this dysbiosis, which can also affect the MGBA and worsen mood disorders (Geng et al., 2020; Madison & Kiecolt-Glaser, 2019).

4. The Role of the Microbiota-Gut-Brain Axis in Disease

4.1. Neurodevelopmental Disorders

Neurodevelopmental diseases, including attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), have been linked more and more to changes in the MGBA. Gastrointestinal symptoms are frequently present in many diseases, indicating a tight connection between brain function and gut health. Distinct gut microbial signatures have been found in ASD, including a decrease in the presence of beneficial genera like Bifidobacterium and Lactobacillus and a rise in Clostridium and Desulfovibrio species (Bundgaard-Nielsen et al., 2020). SCFAs, such as butyrate, are crucial for preserving the blood-brain barrier's integrity, controlling inflammation, and promoting neuronal function. These microbial imbalances, also known as dysbiosis, can interfere with the synthesis of these neuroactive substances. Abnormal SCFA levels may affect synaptic plasticity, neurogenesis, and the expression of genes involved in social behavior and cognition, contributing to the core symptoms of ASD (Checa-Ros et al., 2021). Furthermore, dysbiosis can result in "leaky gut," or increased intestinal permeability, which lets pro-inflammatory chemicals like lipopolysaccharides (LPS) and microbial metabolites enter the bloodstream. By stimulating microglia in the central nervous system, these substances can cause neuroinflammation, a phenomenon linked to both ASD and ADHD. Dopaminergic and serotonergic transmission, which are essential for attention regulation, impulse control, and mood regions that are disturbed in ADHD, may be further compromised by chronic low-grade inflammation and immunological dysregulation (Steckler et al., 2024).

4.2. Psychiatric Disorders

The pathophysiology of anxiety and depression is significantly influenced by the MGBA, mainly because of its impact on immunological, neurochemical, and endocrine pathways that control mood and emotional behavior. The production and availability of important neurotransmitters like serotonin (5-HT), dopamine, norepinephrine, and gamma-aminobutyric acid might be affected by dysbiosis, or an imbalance in the composition of gut microbes (Dziedzic et al., 2024). Under the guidance of particular gut bacteria such as Bifidobacterium infantis and Lactobacillus rhamnosus), enterochromaffin cells in the gut produce about 90% of the body's serotonin. These neurotransmitters and their precursors, such as tryptophan, can directly impact mood, cognition, and stress responses by communicating with the brain through the vagus nerve or systemic circulation. Short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate are also produced by the gut microbiota and have been demonstrated to have anti-inflammatory and neuroprotective properties as well as the ability to pass the blood-brain barrier. SCFAs suppress neuroinflammation, preserve the integrity of the blood-brain barrier (BBB), and regulate microglial activity—all of which are important components in the onset of depression. Increased intestinal permeability, or "leaky gut," caused by dysbiosis makes it possible for bacterial endotoxins such lipopolysaccharides to reach the bloodstream. Through altered hypothalamic-pituitary-adrenal axis activity and neurotransmitter imbalance, LPS activates pro-inflammatory cytokines (e.g., IL-6, TNF-α), causing systemic inflammation and, eventually, neuroinflammation—a well-documented contributor to depressed and anxiety-like behaviors. Additionally, gut microbes tightly regulate the central stress response system, the HPA axis. Dysbiosis can lead to HPA axis hyperactivation, resulting in elevated cortisol levels, which impair hippocampal function, reduce neurogenesis, and exacerbate mood disorders (Ma et al., 2024).

4.3. Neurodegenerative Diseases

Neurodegenerative illnesses, especially Parkinson's disease and Alzheimer's disease, have been linked more and more to dysbiosis, or an imbalance in the gut microbiota. New research shows that an imbalance in gut microbes can cause inflammation in the gut, which can then lead to systemic inflammation and ultimately neuroinflammation. This is a critical factor in the development of neurodegeneration. Multiple disease pathways linked to cognitive and motor decline are caused by disruption of the Microbiota-Gut-Brain Axis (Ashique et al., 2024b).

Increased levels of pro-inflammatory microbial metabolites and decreasing levels of advantageous substances like short-chain fatty acids (SCFAs), especially butyrate, which has anti-inflammatory and neuroprotective qualities, have been linked to dysbiosis in Alzheimer's disease. Butyrate reduces the activation of microglial cells, the immune cells that dwell in the brain, and aids in preserving the blood-brain barrier's (BBB) integrity. A cascade of immunological responses is triggered when the gut microbiota is out of balance because of the increased translocation of lipopolysaccharides (LPS) from the gut into the bloodstream and the decreased synthesis of SCFAs. The pathophysiology of Alzheimer's disease is characterized by persistent neuroinflammation, which is facilitated by these inflammatory chemicals' ability to penetrate the blood-brain barrier or activate the endothelial cells that line it. This inflammatory state is thought to accelerate amyloid-beta (Aβ) plaque formation, impair tau protein clearance, and reduce synaptic plasticity, ultimately leading to cognitive dysfunction (Dandamudi et al., 2024).

Constipation and other gastrointestinal symptoms frequently appear years before motor signs in Parkinson's disease, indicating an early role for the gut in the onset of the illness. According to studies, PD patients have different microbial compositions, with higher levels of pro-inflammatory bacteria (Enterobacteriaceae) and lower levels of anti-inflammatory bacteria (Prevotella, Bifidobacterium). By increasing gut permeability, this microbial change can let bacterial endotoxins and inflammatory chemicals reach the bloodstream. These chemicals may help alpha-synuclein (α-syn) misfold and aggregate in the enteric nervous system, which can subsequently spread to the central nervous system through the vagus nerve. The course of Parkinson's disease is increasingly thought to be caused by this prion-like proliferation of α-syn. The MGBA's role in modulating immune responses, maintaining BBB integrity, and regulating neuronal signaling positions the gut microbiota as a key player in the neurodegenerative process. Dysbiosis disrupts the balance between pro- and anti-inflammatory signals, leading to sustained microglial activation and impaired neuroprotective mechanisms. Additionally, alterations in microbial production of neurotransmitters and their precursors (such as GABA, dopamine, and tryptophan) may further influence neural circuits involved in cognition, mood, and motor function (Philip Mani et al., 2024).

In context of this molecular insight, research on neurodegenerative diseases is increasingly focusing on treatment approaches that target the gut bacteria. The potential of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) to improve cognitive or motor outcomes, lower systemic inflammation, and restore microbial balance is being studied. A neuroprotective microbial profile may also be supported by dietary interventions high in fiber, polyphenols, and fermented foods. These methods are promising non-invasive supplementary therapies to traditional treatments intended to slow or prevent neurodegeneration, but further clinical research is required to confirm efficacy (Dandamudi et al., 2024).

4.4. Metabolic Disorders

The Microbiota-Gut-Brain Axis (MGBA) is a network of interrelated immunological, neuroendocrine, and biochemical processes that have a major impact on metabolic health and obesity. By digesting otherwise indigestible dietary fibers into useable substrates, the gut microbiota plays a critical role in nutrient absorption. In order to increase the amount of energy extracted from food, several bacterial phyla—particularly Firmicutes and Bacteroidetes—are involved in the breakdown of complex carbohydrates and fibers (Cheng et al., 2022). Obese people frequently have a higher Firmicutes-to-Bacteroidetes ratio, which is linked to improved calorie extraction and increased fat deposition and obesity. By affecting host genes involved in lipogenesis and fatty acid oxidation, gut bacteria regulate the intake and storage of lipids in terms of lipid metabolism. Bile acid pool modification by microbial enzymes, such as bile salt hydrolases, influences fat emulsification and micelle formation, which in turn changes lipid absorption. This equilibrium can be upset by dysbiosis, which can lead to lipid buildup in tissues, especially the liver, aggravating diseases like non-alcoholic fatty liver disease (NAFLD). By producing short-chain fatty acids (SCFAs) including butyrate, acetate, and propionate, the gut microbiota also plays a critical role in insulin sensitivity and glucose homeostasis. In addition to lowering hepatic glucose synthesis and stimulating the release of incretin hormones such as glucagon-like peptide-1 (GLP-1), which encourages insulin release and satiety, these SCFAs also improve peripheral tissue insulin signaling pathways. Insulin resistance, a defining feature of metabolic syndrome and type 2 diabetes, is exacerbated by dysbiosis, which lowers SCFA synthesis. Additionally, the generation of neurotransmitters that control behavior, mood, and hunger is influenced by the gut microbiota (B.-N. Liu et al., 2021). For instance, the stomach produces most of the serotonin (5-HT), which regulates mood and satiety signals. Dopamine and gamma-aminobutyric acid (GABA) are two more neuroactive substances that have an impact on reward systems and physical exercise motivation. Thus, behavioral changes like increased hedonic eating, decreased motivation for exercise, and even mood disorders can result from disruptions in microbial composition, all of which feed the obesity cycle (Conlon & Bird, 2014). The vagus nerve, which offers a direct, two-way communication channel between the gut and the brain, is an essential part of the MGBA. Gut hormones and microbial metabolites have the ability to trigger vagal afferents, which send metabolic and satiety signals to the hypothalamus of the brain. These signals may be compromised by dysbiosis, which could result in abnormal appetite control, increased food consumption, and lower energy expenditure. Another important component of this axis is the immune system. When intestinal barrier integrity is compromised by dysbiosis, microbial components such as lipopolysaccharides (LPS) can enter the bloodstream. Toll-like receptor 4 (TLR4) and other pro-inflammatory pathways are activated, which results in chronic low-grade inflammation. The hypothalamus may be impacted by the ensuing inflammation, which could compromise its ability to regulate metabolism and result in leptin and insulin resistance—two factors that are critical to the etiology of obesity. Additionally, the release of important appetite-regulating peptides including peptide YY (PYY) and GLP-1, which both work to reduce hunger and promote fullness, is modulated by the gut flora. In order to promote energy balance and decreased food intake, SCFAs cause the intestinal lining's enteroendocrine L cells to release these peptides. Increased hunger and uncontrolled calorie intake might result from the suppression of this secretion caused by a microbial imbalance. Because of these intricate relationships, MGBA-targeting therapy techniques have become viable methods for managing obesity. According to Yu et al. (2020), Lupien-Meilleur et al. (2020), and Sittipo et al. (2022), probiotics (beneficial bacteria) and prebiotics (non-digestible fibers that encourage beneficial microbial growth) can improve SCFA synthesis, lower systemic inflammation, and restore microbial balance. Furthermore, by reinstalling a healthy microbial ecology, fecal microbiota transplantation (FMT) has demonstrated promise in clinical trials to enhance insulin sensitivity and regulate weight gain. Additionally, MGBA affects motivational states and cognitive processes related to energy balance and weight control. Gut-derived metabolites have an impact on the reward and executive regions of the brain, including the hippocampus and prefrontal cortex, which influence eating habits and physical activity willingness. Neuroplasticity and dopaminergic signaling are adversely affected by inflammation and dysbiosis, which can lower exercise motivation and make it more difficult to maintain good living habits. This multifaceted interaction between gut microbes, the brain, and metabolic organs positions the MGBA as a critical target for therapeutic intervention in obesity and related metabolic disorders (Cheng et al., 2022; B.-N. Liu et al., 2021).

5. THERAPEUTIC IMPLICATIONS

5.1. Microbial-Based Interventions

Taking probiotic supplements and eating prebiotics may alter the makeup and diversity of the gut microbiota, which may benefit mental health and cognitive function. Prebiotics improve overall gut health by giving beneficial bacteria substrates to grow on, while probiotics can alter neurotransmitter systems (Ansari et al., 2023; Victoria Obayomi et al., 2024; Zhou et al., 2024). Fecal Microbiota Transplantation (FMT): FMT has become a viable method for helping people with dysbiosis regain the balance of their gut microbiota. According to preliminary research, FMT may alleviate the symptoms of a number of illnesses, such as obesity and mood problems. Standardized procedures and long-term results require more research (Biazzo & Deidda, 2022; Hamamah et al., 2022; Onifade et al., 2024).

5.2. Lifestyle and Dietary Interventions

Dietary modifications play a critical role in shaping gut microbiota composition. High-fiber diets rich in fruits, vegetables, and whole grains promote the growth of beneficial bacteria, enhancing gut health and potentially improving mental well-being. Additionally, reducing the intake of processed foods and sugar may help mitigate dysbiosis, contributing to better cognitive and emotional health outcomes (Aziz et al., 2024; Conlon & Bird, 2014; Rinninella et al., 2023) .

6. CONCLUSION

A key mediator of physiological processes, the microbiota-gut-brain axis affects metabolic health, exercise motivation, and cognitive function. Gaining knowledge of the complex processes that underlie this axis can help one better understand the etiology of different neuropsychiatric conditions and associated medical conditions. particular MGBA pathways and investigating treatments that target the microbiota to improve mental health, cognitive performance, and general well-being. Further research in this quickly developing area could result in novel approaches to the prevention and management of complicated medical disorders associated with microbial dysbiosis.

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