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# Review Article

# From gut to brain: Deciphering the impact of gut microbiota on neurological health

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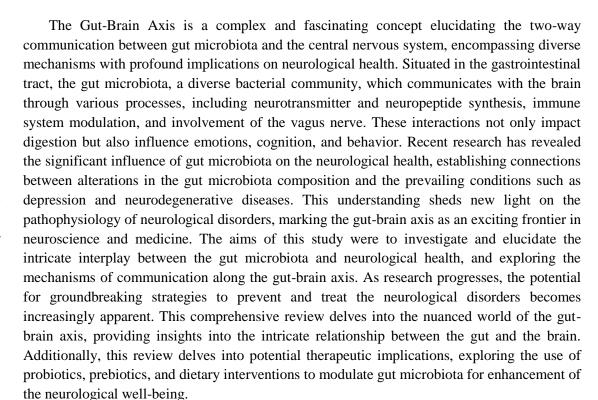
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## **Abstract**



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#### 1. Introduction

The gut-brain axis is a complex and dynamic network that connects the gastrointestinal system with the central nervous system. It is a bidirectional communication system that connects the brain and the spinal cord to the enteric nerve system of the gastrointestinal tract (Wang and Wang, 2016). The gut, its microbiota, the immune system, and the endocrine system are all involved in communication network (El Aidy et al., 2015). The gut microbiota and its impact on the gut-brain axis can vary substantially between individuals. Genetics, diet, and lifestyle all contribute to the individual's gut microbiota's unique makeup and function, which affects the gut-brain axis functions in each person (Ma et al., 2019). The vagus nerve, which sends bidirectional signals between the gut and the brain, provides direct connections between the two. The brain receives information about the gastrointestinal conditions such as nutrient absorption, gut motility, and inflammation for processing (Kuwahara et al., 2020). The gut produces neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA), which are involved in mood control and cognitive function. These neurotransmitters have the ability to alter the mood and the emotions as well as the brain function (Dicks, 2022). Ghrelin and leptin are gut hormones that regulate appetite, satiety, and energy balance. These hormones can also have an effect on the brain functions such as appetite and body weight regulation (Doroszkiewicz et al., 2021). Emerging research suggests that the gut microbiota regulates mood and may influence the prevailing conditions such as depression, anxiety, and stress (Chen et al., 2021). Dysbiosis, or an imbalance in the gut microbiota, has been linked to the neurological disorders like Alzheimer's, Parkinson's, and multiple sclerosis (Liu et al., 2020). The gut microbiota is essential for immune system training and modulation. It aids the immune system in distinguishing between infections and helpful microorganisms. A disruption in the gut microbiota can cause chronic inflammation,

which has been linked to a number of disorders, including those affecting the brain (Ding *et al.*, 2020).

The gut-brain axis allows for continuous communication and synchronization between the gut and the brain, and regulating a variety of physiological and psychological processes (Mukhtar et al., 2019). Several researches have revealed that gut microbiota has a substantial impact on many areas of the neurological health, including cognitive function, mood control, and even neurodegenerative diseases. In the context of neurodegenerative diseases, these researches have uncovered the intriguing connections between alterations in the gut microbiota and the progression of conditions such as Alzheimer's and Parkinson's disease (Bistoletti et al., 2020; Maiuolo et al., 2021). Understanding that the gut-brain axis has implications on the therapeutic approaches, which target the gut microbiota, nutrition, and lifestyle to promote the gastrointestinal and the neurological health. This involves using probiotics and prebiotics, making dietary modifications, transplanting fecal microbiota, and developing specific drugs to control the gut microbiota. Some drugs can affect the gutbrain axis. The antibiotics, for example, may upset the balance of the gut microbiota, potentially harming the brain health (Cammarota et al., 2014). This interaction emphasizes the importance of gaining a thorough grasp of how these drugs may affect this axis. This indepth examination examines the present level of knowledge and addressing the complex relationship between gut microbiota and neurological health. The objective of the study was to analyze the recent research findings that highlight the significant influence of the gut microbiota on the neurological disorders, thus contributing to a deeper understanding of the pathophysiology of the various conditions related to the central nervous system.

# 2. Composition of the human gut microbiota

The types and quantities of bacteria that live in the gastrointestinal tract, which includes the stomach, small intestine, and colon, are referred to as gut microbiota composition (Cryan et al., 2019). The gut microbiota is a rich ecosystem that contains a wide range of microorganisms such as bacteria, viruses, fungi, and archaea (Kandpal et al., 2022). A healthy gut microbiota is diverse, which means that it contains a wide range of bacterial species. This variety is linked to an enhanced overall health. Bacteria are the most prevalent and well-studied microorganisms in the gastrointestinal tract. There are thousands of different bacterial species, with the Firmicutes and the Bacteroidetes being the most common (Kaur et al., 2019). However, the precise composition varies from person to person. The makeup of the gut microbiota varies greatly. Genetics, diet, environment, age, and numerous lifestyle factors all have a role (Oriach et al., 2016). This means that no two people have the same gut microbiota.

Maintaining health requires a stable and resilient gut microbiota. However, several conditions such as antibiotics, illness, and/or a bad diet can upset this delicate equilibrium. While there is an individual variance, several bacterial species are found in the majority of the healthy people. These are frequently referred to as "core microbiota" (Torres-Fuentes et al., 2017). The gut microbiota is dominated by stringent anaerobes, which outnumber the facultative anaerobes and the aerobes by a factor of 100 (Ghanei et al., 2019). Estimates of the number of bacterial species present in the human gut vary greatly between the different researches; however, it is largely acknowledged that people harbor more than 1000 microbial, species-level phylotypes (Clapp et al., 2017). Although the proportional ratios of these phyla may vary, but the Bacteroidetes and the Firmicutes are conserved in almost all people (Mendes et al., 2021). Bacterial cells are scattered irregularly over the length of the gut. The number of bacteria present can range from 10 to 10<sup>3</sup> bacteria/ g of stomach and duodenal contents,  $10^4$  to  $10^7$  bacteria/ g in the small intestine, and to  $10^{11}$  to  $10^{12}$  bacteria/ g in the large intestine (Suganya and Koo, 2020). Furthermore, the microbial community makeup changes between these regions, with distinct bacterial species prevalent in the small intestine and colon. Understanding the makeup and variety of the gut microbiota is an important element of microbiota science study. It has far-reaching ramifications for the overall health and has led to the development of treatment techniques to control and optimize the gut microbiota composition.

## 3. Importance of the neurological health

The total well-being and proper functioning of the nervous system, which includes the brain, spinal cord, and peripheral nerves, is referred to as neurological health (Defaye et al., 2020). The nervous system is a complicated and crucial element of the human body, governing everything from fundamental reflexes to higher cognitive activities. The brain is the major nervous system component in charge of the cognitive functions. emotions. and sensory perception (Oroojzadeh et al., 2022). Maintaining strong neurological health is critical for the overall wellness. Many neurological illnesses can be avoided or postponed by making healthy lifestyle choices. Alzheimer's disease, Parkinson's disease, and stroke are examples of such illnesses (Roe, 2022). Maintaining cognitive function and memory is an important feature of the neurological health, especially as people get older. Puzzles, reading, and acquiring new abilities are all activities that can assist in boosting cognitive well-being. The management and treatments of neurological illnesses are also part of neurological health. Chronic illnesses such as epilepsy and multiple sclerosis, as well as acute disorders such as traumatic brain traumas, are examples of these (Mitrea et al., 2022). The involvement of gut microbiota in neurological health is a new and fastdeveloping area of study. There is still much to learn about the precise processes through which the gut microbiota influences the neurological health. Nonetheless, the gut-brain axis is an interesting area of research, and its potential consequences on the neurological health have important significance for the

future neurology and psychiatry treatments and interventions (Benakis *et al.*, 2020).

# 4. Pathways of communication between the gut and the gut-brain axis

Gut-brain microbiota axis is complex bidirectional communication system that connects the gut, its microbiota, and the central neurological system (i.e., brain and spinal cord) (Zhu et al., 2017). This bidirectional communication is critical in maintaining the overall health and well-being. It is intimately related to the mood and the emotional well-being. The gut microbiota can create neuroactive chemicals that influence memory, learning, and other cognitive functions, resulting in cognitive deficits and possibly contributing to neurodegenerative illnesses (Keightley et al., 2015). Obesity and metabolic problems can result from communication dysfunctions (Sajdel-Sulkowska and Zabielski, 2013). This axis is important in influencing several physiological and psychological processes, and its importance has grown in the recent years. Multiple communication routes, including neurological, endocrine and immunological signaling, are involved in the microbiota gut-brain axis (Silva et al., 2020). The different types of communication pathways have been listed in Table (1).

# 5. Role of gut microbiota in the neurological health

## **5.1.** Cognitive function

The gut-brain axis plays a crucial role in improving the cognitive function as the gut microbiota can influence the production and regulation of several neurotransmitters, such as serotonin, dopamine, and GABA (Manderino et al., 2017). These neurotransmitters are crucial for controlling the mood, and they also have a big impact on the cognitive performance (Socała et al., 2021). Serotonin, for instance, has been shown to affect the memory and learning. Chronic inflammation can result from dysbiosis or an imbalance in the gut microbiota. The serotonin produced in the gut can influence the mood

and behavior. Changes in gut serotonin levels have been linked to conditions like irritable bowel syndrome (IBS) and may contribute to the bidirectional relationship between the gut health and health (Margolis et al., 2021). mental Understanding the role of serotonin in the gut-brain axis provides insights into how the gastrointestinal health can impact the mental well-being and vice versa. This complex interplay emphasizes the holistic nature of health, recognizing the interconnectedness of the various body systems (Serra et al., 2019). Alzheimer's disease and other disorders that impair cognitive function have been connected to chronic inflammation (De la Fuente, 2021). By regulating the systemic inflammation, the gut-brain axis helps to maintaining the cognitive function. The gut bacteria create several metabolites such as butyrate and other short-chain fatty acids (SCFAs) (Dalile et al., 2019). SCFAs can improve the cognitive function and have neuroprotective and anti-inflammatory properties. Particularly butyrate has been demonstrated to support the cognitive health (Majumdar et al., 2023). The blood-brain barrier; a barrier that keeps the bloodstream and brain apart can be affected by the gutbrain axis (Raimondi et al., 2020). Antioxidants produced by certain gut bacteria can shield the brain tissue from the oxidative damage. These antioxidant properties are crucial for maintaining the cognitive health because the oxidative stress can cause cognitive impairment and neurodegenerative diseases (Gwak and Chang, 2021). The generation of neuroactive chemicals and a diverse and well-balanced gut flora has been shown to have neuroprotective effects on the brain (Liang et al., 2018). These benefits may provide protection against neurodegenerative illnesses and cognitive decline (Neri et al., 2023). Through a variety of processes, including neurotransmitter regulation, inflammatory control, and the delivery of vital nutrients, the gut-brain axis affects the cognitive performance (Agustí et al., 2018). Better cognitive health and general brain function can be achieved by supporting the gut-brain axis and keeping the gut microbiota in a healthy state (Wiley et al., 2017).

**Table 1**: Different types of communication pathways

Pathway	Features	References
Neural pathways	<ul> <li>The vagus nerve, which connects the gut and the brain, is critical in bidirectional signal transmission.</li> <li>Data concerning gut circumstances, such as nutrient absorption and gut motility, is transmitted to the brain for processing.</li> </ul>	(Han et al., 2022)
Neurotransmitters	• The gut microbiota can create and regulate the creation of neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are crucial for mood regulation and cognitive function.	( <u>LaGreca et</u> al., 2021)
Hormones	<ul> <li>These neurotransmitters can influence mood, emotions, and brain function.</li> <li>The gut generates hormones that control hunger, satiety, and metabolism.</li> <li>Hormones such as ghrelin and leptin regulate food intake and body weight, and they can have an effect on how the brain controls these processes.</li> </ul>	( <u>Pizarroso et al., 2021</u> )
Cytokines and immune signaling	<ul> <li>Gut microorganisms and their metabolites have the potential to influence the immune system, resulting in the creation of cytokines and immunological responses that affect the brain.</li> <li>Gut inflammation can have an effect on systemic inflammation and brain function.</li> </ul>	(Agirman et al., 2021)
Microbial metabolites	<ul> <li>Metabolites produced by gut bacteria include short-chain fatty acids (SCFAs) such as butyrate.</li> <li>These metabolites have the potential to enter the bloodstream and impact brain function and overall health.</li> </ul>	(O'Riordan <i>et al.</i> ,2022)

## 5.2. Mood regulation

The gut-brain axis significantly influences the emotional health and mood. Distortions in the neurotransmitter levels resulting from dysbiosis of the gut microbiota can impact the mood. Hormones such as leptin and ghrelin, which influence the sensations of hunger, fullness, and general well-being, can alter the human mood (Sun et al., 2020). Leptin is often referred to as the "satiety hormone" because it signals to the brain that the body has enough energy stores, thereby promoting a feeling of fullness and reducing appetite. Meanwhile, Ghrelin, known as the "hunger hormone," that stimulates the appetite and promotes the food intake. Ghrelin levels typically rise before meals and decrease after eating (Woo and Alenghat,

2022). A healthy gut microbiota and appropriate communication along the gut-brain axis can assist in managing the stress and its impact on the mood, which in turn affects the body's stress response (Foster *et al.*, 2017). The expression of genes involved in the emotional regulation and the generation of stress hormones can both be influenced by the gut microbiota (Bear *et al.*, 2021). Anxiety and sadness have been connected to dysbiosis in the gut microbiota (Petra *et al.*, 2015).

## 5.3. Neurodegenerative diseases

Emerging research suggests a strong connection between the gut microbiota and the neurodegenerative diseases (Ghaisas *et al.*, 2016). It is possible that the

pathophysiology of several diseases like Alzheimer's and Parkinson's involves the gut-brain axis. Numerous neurodegenerative illnesses are influenced by chronic inflammation in their early stages (Chu et al., 2021; Sun et al., 2021). The systemic inflammation can be controlled by a healthy gut microbiota and efficient communication along the gut-brain axis (Louwies et al., 2020). Thus, there may be a decrease in the inflammatory load on the brain and a decreased chance of developing neurodegenerative diseases. Due to their neuroprotective properties, the SCFAs may be able to prevent the neurodegenerative illnesses (Moțățăianu et al., 2023). Neurotransmitters such as dopamine and serotonin can be produced and balanced via the gutbrain axis (Qian et al., 2022). Sustaining a robust gutbrain axis may aid in modulation of these neurotransmitters and mitigate the likelihood of several neurodegenerative disorders associated with mood (Yuan et al., 2023). Antioxidants produced by some gut bacteria have the ability to shield the brain tissue from oxidative stress, which is a major cause of neurodegenerative illnesses (Dumitrescu et al., 2018). These antioxidants may aid in preventing or delaying the onset of such illnesses by lowering the oxidative stress.

# 6. Therapeutic implications of the gut-brain axis

Gaining knowledge of the gut-brain axis has made the therapeutic approaches more feasible (Quigley, 2005). Altering the gut microbiota and brain lifestyle communication, adjustments, dietary adjustments, and the use of probiotics and prebiotics can help to treat these neurological conditions (Thangaleela et al., 2022). Personalized therapies are emerging as a result of our growing understanding of the unique characteristics of the gut-brain axis. The goal of precision medicine techniques is to customize the interventions to the person's particular genetic makeup, lifestyle choices, and gut microbiota composition (Evrensel and Tarhan, 2021). It is noteworthy that although the therapeutic implications of the gut-brain axis hold great promise, further study is necessary to confirm the safety and effectiveness of many of these approaches. Some of these potential approaches include:

#### 6.1. Probiotics

Probiotics are live microorganisms, usually good bacteria that are taken orally to support the preservation or restoration of the normal gut microbiota balance (Kesika et al., 2021). Probiotics may enhance the gut health and thus have an impact on the gut-brain axis by encouraging the growth of beneficial bacteria (Westfall et al., 2017). Certain probiotic strains have the capacity to create moodregulating neurotransmitters like GABA and serotonin. Additionally, they have anti-inflammatory properties that aid in lowering the long-term intestinal inflammation (Dahiya and Nigam, 2022). These probiotics may be advantageous to the general wellbeing and may have an effect on the brain health, since high levels of inflammation are associated with a number of neurological disorders.

#### 6.2. Prebiotics

Prebiotics are indigestible dietary fibres and substances that nourish the good gut flora (Lasrado and Rai, 2022). They aid in promoting the development and activity of particular good bacteria in the digestive system by acting as a source of food for these bacteria (Hyland and Stanton, 2023). This may result in a more favorable makeup of the gut microbiota, which will benefit the gut-brain axis. Hormones that control hunger and weight, such as ghrelin and leptin, can be influenced by prebiotics (Joshi et al., 2018). Prebiotics can lower the risk of several gut-related problems that may impact the general well-being and the gut-brain axis.

#### **6.3. Diet**

In terms of the therapeutic implications of the gutbrain axis, diet is very important. Foods have an impact on the composition of gut microbiota, metabolite synthesis, and overall gut health, all of which are related to the brain function and mental health (Sandhu *et al.*, 2017). A diet rich in fiber from

whole grains, legumes, fruits, and vegetables encourages the development of good gut bacteria and ads to the diversity of the gut microbiota. Prebiotic fiber feeds the good bacteria that have a beneficial effect on the gut-brain axis. Consuming foods high in probiotics, such as kefir, sauerkraut, kimchi, and yogurt, can help the gut to become colonized with healthy living microorganisms (Barber et al., 2021). Berries, dark chocolate, tea, and red wine are foods high in polyphenols, which have anti-inflammatory and antioxidant properties (Brewer-Smyth, 2022). They can have a good impact on the gut-brain axis by lowering the inflammation and oxidative stress, which are linked to a variety of brain illnesses. Omega-3 fatty acids, which can be found in fatty fish such as salmon, walnuts, and flaxseeds, have neuro-protective properties (Ghosh, 2021). An anti-inflammatory diet low in processed foods, sweets, and saturated fats can help to lower the systemic inflammation, which benefits both the gut and the brain health (Berding et al., 2021a). The Mediterranean diet, which is high in fruits, vegetables, olive oil, and seafood, has been linked to a lower incidence of cognitive decline and mood disorders (Ağagündüz et al., 2023). Fasting and intermittent fasting have been demonstrated to improve the gut health and the gut-brain axis. Hydration is critical for the gut health as well as the overall body function (Berding et al., 2021b). These dietary recommendations may have therapeutic implications for maintaining a healthy gut-brain axis and promoting the mental and neurological health.

# 6.4. Lifestyle

Lifestyle decisions can have a significant influence on the gut-brain axis and its therapeutic implications on the overall health (Donoso et al., 2023). Regular exercise has been demonstrated to have a favorable effect on the gut-brain axis. Chronic stress can alter the gut-brain axis, causing gastrointestinal difficulties as well as mental health disorders. Proper sleep is required for a healthy gut-brain axis (Skonieczna-Żydecka et al., 2018). Sleep disruptions can affect the composition of the gut microbiota and increase the risk of mood disorders. Individuals can actively support the

gut-brain axis and improve the general well-being by making beneficial lifestyle choices. These options are frequently used in conjunction with dietary and therapeutic interventions, and they can have a substantial impact on the prevention and management of the gut-related and neurological diseases (Naveed *et al.*, 2021).

## **6.5.** Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation (FMT), often known as fecal transplant, is a medical treatment that involves transplanting of fecal materials having a healthy gut microbiota from a healthy donor into the gastrointestinal tract of a recipient (Hu et al., 2022). FMT offers therapeutic potential for the gut-brain axis and has received much interest in the gastrointestinal and neurological medicine (Zhu et al., 2023). FMT is generally used to restore the healthy gut microbiota in people who have gut dysbiosis, such as those with Clostridium difficile infection, Inflammatory bowel disease (IBD), and/ or Irritable bowel syndrome (IBS) (Limas-Solano et al., 2020). FMT may help improve the gut health by re-establishing a healthy gut microbiota, and hence regulate the gut-brain axis. It has the potential to introduce the beneficial gut bacteria into the recipient's gut. These bacteria may create metabolites with anti-inflammatory and neuroprotective properties, such as SCFAs. FMT is a tailored treatment, therefore choosing an appropriate donor is critical (Hillestad et al., 2022). The goal is to pair the recipient with a healthy donor whose gut microbiota makeup promotes the gut health and wellbeing. This tailored approach has the potential to improve the therapeutic effects on the gut-brain axis.

# **6.6. Targeted medications**

In the study of the gut-brain axis, targeted drugs are a new area of research and development, which are intended to target and alter the gut microbiota or their communication with the brain in order to treat a variety of health conditions (Leprun and Clarke, 2019). Table (2) shows a list of some of the most important prospects of the tailored therapy.

 Table 2: Types of target medications influencing the gut-brain axis

Medicine	Features	References
Psychobiotics	Psychobiotics are live	(Kavvadia <i>et al.</i> , 2017)
	microorganisms, similar to	
	probiotics that have the ability to	
	influence brain function and mental	
	wellness. They are chosen for their	
	capacity to generate neuroactive	
	chemicals, impact neurotransmitter	
Microbial metabolite	synthesis, and reduce inflammation.  To alter the gut-brain axis,	(Van de Weyn, et al. 2017)
modulators	To alter the gut-brain axis, medications that target specific	(Van de Wouw <i>et al.</i> , 2017)
modulators	microbial metabolites, such as	
	SCFAs or neurotransmitter	
	precursors, can be employed. These	
	drugs are designed to control the	
	levels of metabolites that affect	
	mood, cognitive function, and brain	
	health.	
Gut barrier enhancers	Medication that targets specific	(Alonso <i>et al.</i> , 2014)
	microbial metabolites, such as	
	SCFAs or neurotransmitter	
	precursors, can be used to change the	
	gut-brain axis. These medications are	
	intended to regulate the levels of metabolites that influence mood,	
	cognitive function, and brain health.	
Neurotransmitter	Medications designed to modulate	(Mittal et al., 2017)
modulators	the production and regulation of	(Wittair & at., 2017)
ino d diators	specific neurotransmitters. These	
	medications may influence	
	neurotransmitter balance and	
	improve mental well-being.	
Immunomodulators	Medications that target the immune	(Hemarajata and Versalovic, 2013)
	system and lower gut inflammation	
	may have an indirect effect on the	
	gut-brain axis. These drugs can	
	improve brain health and potentially	
	lower the risk of neuroinflammatory diseases by reducing chronic	
	inflammation.	
Bacterial signaling	Immunomodulators and anti-	(Hampl and Stárka, 2020)
disruptors	inflammatory medications may have	(Trampi and Starka, 2020)
uisi up to is	an indirect influence on the gut-brain	
	axis.	
	By lowering chronic inflammation,	
	these medications can improve brain	
	health and potentially lessen the risk	
	of neuroinflammatory disorders.	

#### Conclusion

The gut-brain axis is a fascinating area of research that has revealed the substantial influence of the gut microbiota on the neurological health. A balanced and diverse gut microbiota is crucial for maintaining the cognitive function, regulating the mood, and potentially preventing the neurodegenerative diseases. As our understanding of this complex relationship deepens, it opens up exciting possibilities for novel therapeutic interventions that may improve the lives of those individuals with neurological disorders. However, more research is needed to fully comprehend the intricacies of the gut-brain axis and its therapeutic potential.

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#### **Conflict of interests**

There are no conflicts of interest to declare.

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## **Ethical approval**

None-applicable.

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Conceptualization: R.G., A.D.; Investigation: G.S; Supervision: R.G., M.A.; Writing, reviewing, and editing: R.G., A.D., M.A and G.S.; Roles/Writing - original draft: R.G.

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