

GUT FEELINGS: THE ROLE OF THE MICROBIOME IN BRAIN FUNCTION AND BEHAVIOR - SYSTEMATIC REVIEW

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ABSTRACT

Background: The gut microbiome is a very dynamic and complicated ecosystem that has a key role to play in the regulation of the brain and behavior through the use of the gut-brain axis. This two-way communication system affects neurological development, mental health, thinking, and behavior through immune signaling, microbe-derived metabolites, neurotransmitters, and through Vagal circuits.

Objective: The purpose of this systematic review is to summarize the existing evidence of the effect of gut microbiome on brain functioning, the way it develops over different stages of life, its involvement in mental disorders, and the possibility of therapy based on microbiome regulation.

Methods: Following the PRISMA requirements, the literature was searched in the PubMed, Scopus, and Web of Science databases and limited to the period of 2015-2025 to find the studies. Articles that focused on associations between gut microbiota, gut-brain axis, neurodevelopment, neurodegeneration, psychiatric diseases, and microbiome-based treatments were included in the review.

Results: The review points to several mechanisms by which the gut microbiome influences the brain, one of them being short-chain fatty acid (SCFA) production, neurotransmitter production, immune regulation, and the vagal pathway. The brain maturation and cognitive outcomes depend on early-life microbiome composition, which has a profound influence. There is a lot of evidence of an intense relationship between dysbiosis and neurodevelopmental, neuropsychiatric, and neurodegenerative conditions. Probiotics-based interventions, prebiotic interventions, dietary modulation, and fecal microbiota transplantation all hold therapeutic promise.

Conclusion: The gut microbiome makes considerable contributions to the regulation of brain activity and behavior throughout the life cycle, and these connections are complex physiological mechanisms. Although proceeding research suggests new treatment possibilities in neurological and psychiatric diseases, some difficulties are associated with methodological heterogeneity, variability of microbiome in different people, and a lack of understanding of the mechanisms.

1. INTRODUCTION

Various microorganisms have a very diverse and dynamic ecosystem in the human gastrointestinal tract, collectively known as the gut microbiome. This complicated community consists of trillions of bacteria, viruses, fungi, archaea, and many other microorganisms, which are ten times greater than human cells ^{[1][2]}. Gut microbiome is not an inert set of microbes hunting in the intestines but an integrated component of a functioning organ that has a tremendous impact on human physiology, metabolism, and well-being ^[3]. The gut microbiome composition is largely dominated by four main types of bacterial phyla, including Firmicutes (60-65% of the total number of bacteria), Bacteroidetes (20-25%), Actinobacteria (3-10%), and Proteobacteria (1-5%) ^[4,5,6]. In such phyla, particular genera are critical to homeostasis: Firmicutes hosts useful genera, *Clostridium*, *Lactobacillus*, and *Enterococcus*; whereas Bacteroidetes hosts valuable taxa, *Bacteroides* and *Prevotella* ^[2,7]. The great plasticity and resilience of this microbial ecosystem are exhibited throughout the human lifespan. The gut microbiome is constantly developing, maturing, and adapting to changes presented in the form of several different factors ^[3]. The plasticity of the gut microbiome enables the ability to adapt to dietary modifications, drugs, stressors, and environmental triggers and continue their fundamental activities that are already fundamental to the health of humans ^[6].

GUT-BRAIN AXIS AS A BIDIRECTIONAL COMMUNICATION SYSTEM

The notion of the gut-brain axis can be considered as one of the greatest Realizations of contemporary neuroscience and microbiology. This two-way dialogue system connects the gut and the central

nervous system in a complicated chain of neural, hormonal, immune, and metabolic responses ^[8,9,10]. Crosstalk between the brain and the gut microbiome occurs continuously through the gut-brain axis that affects behaviour, cognition, emotion, and neurological function ^[11,12,13].

The anatomical support of the gut-brain axis consists of some main aspects. The enteric nervous system (ENS) or the so-called second brain has about 250 500 million neurons embedded in the gut wall ^[14,15]. This gigantic nervous system functions with a rather high degree of autonomy and is connected with the central nervous system via the vagus nerve, sympathetic, and parasympathetic pathways ^[16,17,18]. The two-way relation has far-reaching consequences in pathophysiological implications of neurological and psychiatric disorders and establishing new forms of therapy ^{[8][19][20]}.

2. COMPOSITION AND DEVELOPMENT OF THE GUT MICROBIOME

Microbial Diversity and Major Bacterial Phyla

The human gut microbiome is ranked as one of the richest and complicated biomes on the planet, with an estimated number of different bacterial species of 1,000-1,500 and a total genome of more than 3 million genes ^{[7][3]}. The Firmicutes phylum is the highest percentage of gut microbe (60-65%) and consists of many genera which are of utmost importance to human health ^{[4][5]}. An important representative is *Clostridium* clusters IV and XIVa, which are the main butyrate producers because of dietary fiber fermentation ^{[21][4]}. Species of *Lactobacillus* in this phylum are important in the production of lactic acid and resistance to pathogens, whereas species of *Enterococcus* are involved in immune modulation ^{[22][4]}. Other significant

Firmicutes SCFA-producing genera, which exist in the Firmicutes, are Roseburia, Eubacterium, and Faecalibacterium, and are vital in keeping the barrier of the gut intact and offering energy to colonocytes [23][21].

The second most dominant phylum is Bacteroidetes (2025%) and it specialises in the complex polysaccharide and plant-derived carbohydrates breakdown processes [2]. The Bacteroides genus is more specialized in degrading food fiber and fermenting it to develop acetate and propionate as the most significant products of metabolism [1][24].

Factors Influencing Microbiome Development

Gut microbiome development and composition are dependent on a variety of factors, which occur before and after birth. Learning more about these factors is essential to the process of understanding how the microbiome of the gut influences the health of humans and their vulnerability to disease.

Prenatal and Birth-Related Factors

One important source of such influences is the maternal environment during pregnancy, and maternal diet, stress, antibiotic exposure, and health influence the intrauterine environment, which therefore has effects on fetal microbiome priming [25][26]. The maternal microbiome may also play a role in fetal neurodevelopment by producing metabolites that diffuse across the placental barrier and cause an alteration in fetal development [27,28].

Postnatal Factors

Early development of the microbiome is greatly affected by feeding practices. Breastfeeding also enhances the development of Bifidobacteria species by the delivery of the human milk oligosaccharides (HMOs) as selective

prebiotics of the beneficial bacteria [44][50]. Breast milk also possesses positive bacteria, antibodies, and immune factors that cultivate the infant microbiome [50][51]. Infants that get formula-fed tend to have a higher microbial diversity at an earlier age and possibly higher populations of pathogenic organisms [25,29].

Dietary And Lifestyle Factors

Diet is one of the most adaptable contributors to the microbiome composition of adults. Fiber- and plant-rich diets also encourage probiotic bacteria of the types SCFA-producers, including Roseburia, Bifidobacteria, and Bacteroides [21,24] to thrive. It is established that proton pump inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and metformin reshape the microbiome of the gut. These drugs can change the gut milieu and favor certain populations of bacteria and discourage others [22,32].

3. GUT MICROBIOME NEURODEVELOPMENT

Impact of Early-Life Microbiome Composition on brain development, synaptic plasticity, and cognitive outcomes:

The early-life stage is a sensitive period in which the impact of the gut microbiome has holistically and permanently significant impacts on the development of the brain, synaptic plasticity, and cognitive outcomes [33][27][30]. The rest of early development, commonly known as the first 1000 days, includes pregnancy, birth, and the first two years of life, where both microbiome and nervous system are rapidly maturing and forming patterns that remain lifelong [30][31][34].

Critical Windows of Development

This theory of critical windows of neurodevelopment has been expanded to

incorporate the outcomes of microbiome-mediated influences on brain maturation. The vulnerable brain at these sensitive times is especially sensitive to its environmental conditions, such as cues of the gut microbiome ^{[27][30][34]}.

- **Prenatal factors:** Recent studies have shown that the makeup of the microbiome in a mother during pregnancy has the potential to affect the development of the brain in an unborn child in the form of creating metabolites which can pass through the placenta ^{[27][26][35]}. The bacteria of the intestines of the mother synthesize short-chain fatty acids, neurotransmitters, and immune mediators that would influence the neurodevelopment of the fetus before birth ^{[27][26][35]}.
- **Perinatal colonization:** The original colonization of the infant intestine is an important phase in the creation of links between the microbiome and the brain. Early life delivery, feeding, and prenatal exposure to the environment are likely to have long-lasting impacts on both the microbiome and brain formation ^[29,30,33].
- **Infancy and early childhood development:** The high rates of growth and maturation of the brain and microbiome occur during the 6-month to 3-year period of life. This time coincides with the formation of stable microbial communities, which critically form neurodevelopment milestones such as language development, socialization, and formation of cognitive skills ^[30,31,33].

Cognitive Outcomes and Microbiome Composition

The correlation between childhood-age microbiome profile and cognitive outcomes in adulthood has been observed in animal models and humans ^{[33][27][30]}.

- **Language development:** Several reports have found a correlation between certain gut bacteria and language development among children. As an octave, increased *Bacteroides* and *Bifidobacterium* presence were linked with language ability and communication process improvement ^{[25][33][30]}.
- **Social behavior:** The gut microbiome may also be associated with social behavioural development, with some microbial profiles being linked to better social behaviours and fewer autism-like behaviours. This association could occur mediated by effects on neurotransmitter systems and formation of neural circuits ^{[33][35][36]}.
- **Cognitive flexibility:** Composition of the gut microbiota may affect cognitive flexibility and the development of executive functions. Greater diversity and other particular bacterial taxa have been linked to superior mental flexibility and problem-solving skills ^{[37][30][38]}.
- **Attention and hyperactivity:** Gut microbiome can potentially play a role in the development of attention and hyperactivity, where some bacteria give way to improved attention regulation that occurs and decreased hyperactivity. This can be via neurotransmitter channels and stress mechanisms ^{[30][31][36]}.

Human Studies Linking Microbiome Alterations to Neurodevelopmental Trajectories

The findings implicating changes in gut microbiome in neurodevelopmental outcomes can be traced both to evidence gleaned in the context of controlled animal research and to observational studies in humans, thus offering a holistic picture of such relationships^[33,27, 30].

Human Population Studies

In human research, the relevance of animal discoveries with respect to human neurodevelopment has been established but is bound by ethical and logistical reasons^{[25][33][27]}.

- **Birth cohort studies:** Birth cohort studies are supersized to trace children since their birth to assess the correlation between early microbiome structures and subsequent neurodevelopmental outcomes. This work has already found a couple of special taxa correlated with cognition and behavioural outcomes^{[25][33][27]}.
- **Preterm infant studies:** Studies among preterm infants have shown information on the association between microbiome development and neurodevelopment in the infants. Such investigations have demonstrated an ability to indicate future neurodevelopmental profiles in this at-risk group based on the state of their microbiome at an early age^{[33][29][39]}.
- **Autism spectrum disorder research studies:** Research comparing the composition of the gut microbiome in children with autism spectrum disorders to children who develop typically has demonstrated large differences. The research has detected certain bacterial strains that could cause autism behaviour^{[35][36][40]}.

- **Studies on attention deficit hyperactivity disorder (ADHD):** ADHD studies in children found that the microbiome differs in children with ADHD as compared to healthy individuals, and that the differences could help explain attentional and hyperactivity symptoms. According to these studies, interventions involving the microbiome look like they could help with ADHD management^{[30][31][36]}.

Clinical Implications and Future Directions

Investigations of the microbiome-based shifts within the framework of neurodevelopmental pathways have practical clinical value and are the best fields of further research.

- **Early intervention opportunities:** The collection of critical windows in the microbiome-brain interactions implies that early interventions could be especially successful in the prevention or treatment of neurodevelopmental disorders. Examples of such interventions may involve the intervention of probiotics, dietary interventions, or microbiome-specific interventions.
- **Personalized medicine solutions:** The high level of individuality of the microbiome composition linked with neurodevelopmental consequences implies that they require individualized treatment. The studies in the future are aimed at finding personalized factors modulating the microbiome-brain interactions.
- **Preventive measures:** Identifying those factors that determine the early microbiome may result in

preventive measures for neurodevelopmental disorders. These interventions could comprise fine-tuning the maternal community of microbes as per pregnancy or encouraging a positive community of microbes in the early years of life [33][30][31].

4. GUT MICROBIOME IN MENTAL HEALTH AND BEHAVIOUR

Depression and Stress: Evidence of Gut Dysbiosis in Psychiatric Disorders

The connection between mental illness and the intestinal microbiome structure has become one of the most convincing fields of investigation of the gut-brain axis. There is compelling evidence illustrating that patients with an anxious, depressed, or stress-related illness display unique dysbiosis patterns of the gut, which could play a part in the development and sustenance [41][28][42].

Microbiome Alterations in Depression

The characteristics of changes in the composition of the microbiome of the intestines are specific to patients with major depressive disorder (MDD) compared with healthy controls. These changes are both reductions of beneficial bacteria and increases of possible pathogenic species.

Depression is a proposed mechanism of action that involves components of the bowel flora and the host immune system, which combine to produce Belfast, the functional equivalent of root anti-inflammatory drugs that produce significant changes in beneficial bowel bacteria, including Bifidobacteria (GABA-producing and anti-inflammatory), Lactobacillus species (mood regulating), Faecalibacterium prausnitzii (pro-butyrate,

anti-inflammatory), and Roseburia species SCFA. Equally, anxiety is linked to a reduction of GABA-producing bacteria such as: Bifidobacterium adolescents, B. longum, Lactobacillus rhamnosus, L. helveticus, and Enterococcus species.

Dysbiosis associated with anxiety is also characterized by a decrease in clusters of Clostridium sensitive to cortisol, elevated Bacteroides (adapted to stress), and an increase in Prevotella (linked to stress-related concerns). Additionally, inflammatory bacteria like Enterobacteriaceae and Proteobacteria are more prevalent, while beneficial Akkermansia muciniphila is reduced, leading to inflammation and negatively affecting mental health outcomes. [28, 41]

Stress-Related Microbiome Changes

Chronic stress is a major factor in the evolution and continuation of anxiety and depression, as well as being constantly linked to specific disorders of the gut microbiome, which may provide stability of the indicators of mental health. Stress-related dysbiosis. Chronic stress predictably alters the composition of the microbiome, elongated known as reduced microbe diversity, reduction in useful bacteria like Lactobacillus and Bifidobacterium, and the advancement of potentially pathogenic microorganisms, in particular, Enterobacteriaceae. Moreover, the effect of chronic stress is regularly associated with the aberrant figure of Firmicutes/Bacteroides. These alterations are tightly related to the hypothalamic-pituitary-adrenal (HPA) axis since bacteria that colonize the microbiome may facilitate cortisol production as well as sensitivity. Chronic stress and dysbiosis that comes along with it also has the potential to weaken the integrity of the gut barriers, which work as a result of increased

intestinal permeability (popularly known as leaky gut), thus enabling the transfer of bacterial products to the rest of the body, hence fostering systemic inflammation. Such inflammation may, in its turn, lead to the occurrence and maintenance of mental health symptoms ^{[43][44][26]}.

Cognitive Function and Emotional Regulation: Microbial Influence on Neurotransmitter Systems

The microbiome of the gut has extensive effects on the functions of the brain and mood by having direct and indirect impacts on neurotransmitter systems.

Serotonin System Modulation:

Serotonin is one of the most significant neurotransmitter systems on which the gut microbiome affects, and estimated that 90 percent of the body's serotonin is made in the GI system.

- **Production in microbes:** Although the intestinal microbes are not able to produce serotonin directly, they can play major roles in the way the serotonin is produced by enterochromaffin-type mystery cells. Species of *Enterococcus* and *Streptococcus* can produce precursors and co-factors necessary in the process of production of serotonin; some species of *Lactobacillus* increase the availability of tryptophan, which also facilitates the production of serotonin. Also, other bacteria capable of producing SCFAs can activate the enterochromaffin cells to enhance the synthesis of serotonin.
- **Tryptophan metabolism:** The bacteria of the gut compete over the precursor of serotonin, tryptophan, and the outcome of this competition affects its metabolism. Most

bacteria can promote the use of tryptophan to synthesize serotonin, where beneficial bacteria can encourage this process, and pathogenic bacteria can redirect it towards the kynurenine pathway. These pathways have a significant role to play in mood and cognitive regulation by balancing with each other.

- **Serotonin transport and metabolism:** Gut bacteria may modulate serotonin transport and metabolism in several ways, such as the regulation of serotonin transporter expression, the modulation of the enzymes that break down serotonin, as well as the sensitivity of the serotonin receptors ^{[16][11]}.

GABA System Interactions:

Gut and brain interaction Behaviors The gut bacteria can directly affect the GABAergic system, which is important in the regulation of anxiety and cognitive ability in humans.

- **Direct GABA production:** A few of the gut bacteria can direct GABA production. *Lactobacillus brevis* and *Lactobacillus plantarum* are reported to produce high levels of GABA, and *Bifidobacterium* species, especially *B. adolescentis*, play a role in producing GABA. *Enterococcus* species, furthermore, also contribute to the production of GABA in the gut.
- **GABA receptor influencing:** Gut bacteria can affect the GABA receptor gene and also feature through several pathways. Short-chain fatty acids (SCFAs) are capable of augmenting the sensitivity of the GABA receptors, and anti-inflammatory bacteria also maintain the integrity of the GABA

receptor actions. Moreover, some GABA receptor modulators may be conducted by certain bacterial metabolites ^{[16][11]}.

- **Glutamate- GABA balance:** Gut microbiome is very important in maintaining brain balance between the excitatory glutamate and the inhibitory GABA signaling. When the bacteria are beneficial, they can enhance the production of GABA and decrease glutamate levels, but dysbiotic bacteria might move the balance to too much excitation. It is this equilibrium that is important to the regulation of anxiety and cognitive activity ^{[16][11]}.

Dopamine System Modulation:

Gut microbiota has several effects on the dopaminergic system, which is critical in motivation, reward processing, and motor functions.

- **Bacterial production of dopamine:** One of the causes of dopamine is that certain bacteria in the gut can make dopamine and similar products. The *Bacillus* species can synthesize dopamine out of L-DOPA, and *Enterococcus* species synthesize dopamine precursors, and some of the *Clostridium* species are also involved in dopamine metabolism.
- **Availability of Dopamine precursors:** Gut micro-organisms affect the supply of Dopamine precursors in several ways. The availability of tyrosine and L-DOPA can be affected by bacterial metabolism, where binding and availability of the precursors could be increased by beneficial

bacteria and suppressed by the inflammatory bacteria.

- **Modulation of dopamine receptors:** Gut microbiome can affect the expression and function of dopamine receptors in several ways. Short-chain fatty acids (SCFAs) can make dopamine receptors sensitive, and anti-inflammatory bacteria can be protective against dopamine neurons, as well as some bacterial metabolites can regulate the activity of dopamine ^{[16][11]}.

5. CHALLENGES AND FUTURE DIRECTIONS:

There are astonishing inter-individual differences in the microbial composition of the gut, which have enormous consequences on the efficacy of microbiome-based treatment and make it challenging to develop generalized treatment ^{[45][3]}. The variability is determined by multifactorial interactions between genetic, environmental, and lifestyle factors that determine the microbiome composition and functions over the course of life.

Genetics of Affecting Microbiome Diversity:

Genetically, the host determines the composition and functioning of the microbiome, and some genetic variants have been found to highly impact the abundance and diversity among the bacteria ^{[45][3]}. Human leukocyte antigen (HLA) system: Human leukocyte antigen (HLA) system plays a key role in the immune system and thus plays a significant role in the microbiome composition ^{[45][3]}.

- Disparate HLA haplotypes are linked to various bacterial communities
- Elite immune responses in the case of particular bacterial species are influenced by HLA variants
- The difference in microbiome-mediated susceptibility to diseases may be attributed to these genetic differences
- Certain interventions might require a consideration of HLA status on an individualised basis

Cytokine gene polymorphisms: Cytokine gene polymorphisms influence the inflammation responses and microbiome [45][3].

- Morphisms of the IL-10 gene determine responses to anti-inflammatory signals
- Variants of the TNF gene modify pro-inflammatory signaling
- The same genetic variations can affect the success of anti-inflammatory interventions
- Genetic testing can be used to pre-determine responses to treatment

CONCLUSION

The gut microbiome is an essential regulator of brain and behavior because it has a complex pathway of interaction with the gut-brain system. Findings of this systematic review raise the evidence that has a considerable impact on neurodevelopment, cognition, and mental health through gut microbial composition. Disruptions of the intestinal microbiome, through childhood events, diet, drugs, or exposure to the environment, have a strong correlation with the pathophysiology of disorders like autism spectrum diseases,

ADHD, depression, anxiety, or neurodegenerative diseases.

Targeted manipulation of the gut microbiome by means of therapeutic measures might become a promising tool in the treatment and even prevention of many neuropsychiatric and neurodevelopmental disorders. Nevertheless, it is difficult to establish the translation of these findings in the standardized clinical practice because of the extensive inter-individual variability, the absence of longitudinal research, and the inadequate definition.

It is preferred that future studies should be well-designed, large-scale longitudinal studies in a bid to understand the causal relationships and also narrow down personalized microbiome-based therapy. One of the issues that scientists must understand better is the complex interplay between host genetics, microbiome, and environmental factors to unlock new treatments for brain disorders that have their foundation based in the gut-brain axis.

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