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A Review on "Bidirectional Communication Between Gut-Microbiome-Brain Axis and its Influence in Brain Disorders"

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ABSTRACT

The microbiota-gut-brain axis serves as a bidirectional communication system between the gastrointestinal tract and the central nervous system. Within the intestines lies a highly complex ecosystem comprising over 100 trillion microbial cells, inhabiting both the small and large intestines. This dynamic interaction between the gut microbiota and the intestinal lining can bring about physiological changes in the brain, influencing mood and behavior. Recent attention has been dedicated to investigating the impact of these interactions on mental health, with compelling evidence suggesting the involvement of gut microbiota in various neurological and psychiatric disorders. This review thoroughly explores how gut microbiota can affect the brain and behavior in conditions such as Alzheimer's disease, dementia, anxiety, autism spectrum disorder, Parkinson's disease, and schizophrenia. The focus primarily centres on the pathways associated with intestinal metabolites produced by these microbes, encompassing neural pathways, the immune system, and chemical transmitters, which contribute to the development of these disorders. Furthermore, the review underscores the clinical evidence supporting the potential of prebiotics, probiotics, and fecal microbiota transplantation as adjunct therapies for neuropsychiatric disorders.

1. INTRODUCTION

In the past decade, a lot of work has been made in understanding the function of the bidirectional interactions between the brain, the gastrointestinal tract, and the gut microbiota, mostly based on investigations with experimental animals. Research employing experimental animals has demonstrated how the gut microbiota influences affective, social, nociceptive, and ingestive behaviors. All creatures, including humans, have a close relationship with microbial communities, which are made up of bacteria, archaea, fungi, and viruses. The microbiota, or groups of bacteria, live on almost every surface of the body that is exposed to the environment. The gut microbiota, or community in the gastrointestinal tract, is the most numerous and densely populated microbiota in the human body. Numerous studies have shown that the gut microbiota is vital to the health of our immune systems[1], metabolism[2], and even the development of different organs[3], rather than just being passive participants in our bodies. Gut bacterial populations are dynamic organisms that can change throughout our lives as well as in response to host factors like age and genetics[4] as well as altering environmental factors, with diet[5] and medications[6] being the primary causes. Although Gut microbiota research encompasses the study of various microorganisms, such as fungi, archaea, and viruses. However, the primary focus of this review lies in the analysis of bacteria, as it is the source of the most extensive information, Bacteria found in gut microbiota equal to several human cells in the body[7]. To date, *Firmicutes spp*. and *Bacteroides spp*. are known to be the most common, accounting for 3/4 of all intestinal microbiomes [8].

The term "gut-microbiota-brain axis" refers to a network of relationships among many biological systems that enables bidirectional communication between gut bacteria and the brain. This communication is essential for maintaining the homeostasis of the gastrointestinal, central neurological, and microbial systems of animals. These biological network communication channels include direct and indirect signaling through neural pathways, the immune system, and chemical transmitters[9,10]. The scope of this axis has been broadened to include the microbiota, now referred to as the microbiota-gut-brain axis. Fascinating findings have emerged, suggesting that the bacteria residing in the gut could potentially influence the central nervous system. As a result, the microbiome has emerged as a potential diagnostic and therapeutic target in disorders as diverse as Parkinson's disease,

Alzheimer's disease, amyotrophic lateral sclerosis, autism, stroke, depression, and drug addiction[11].

Numerous studies linking microbial communities and their function to neuropsychiatric disorders associated with development (such as schizophrenia and autism spectrum disorder (ASD)[12] , mood (such as depression[13]and anxiety), and neurodegeneration (such as Parkinson's disease[14], Alzheimer's disease and multiple sclerosis) have been conducted as a result of this new perspective. Simplified animal models, which have limitations in their ability to accurately represent the intricacies of human disease, have been heavily used in research to understand these links. Recent technological advancements are striving to go beyond just observing correlations and instead concentrate on discovering and verifying the biological mechanisms that can effectively treat human diseases. However, it is crucial to acknowledge that extensive validation of the links between gut microbiota and neuropsychiatric disorders is currently limited [15].

2. The microbiome in health: Development, influence, and Function

The gut microbiota exhibits extensive diversity and individual variation when examined at the level of bacterial strains. However, when observed at higher organizational levels, certain predominant patterns emerge. Specifically, two phyla, *Firmicutes* and *Bacteroidetes*, dominate the human gut. Additionally, populations can be categorized based on the prominence of specific species, namely *Prevotella, Bacteroides, or Ruminococcus*[16]. These groups of species are termed enterotypes, and their relative prevalence is thought to be primarily influenced by dietary factors [16,17].

Recent evidence suggests that the colonization of an infant's gut might begin during the prenatal stage from the placenta. However, the majority of the infant's microbiota is acquired from the mother during childbirth, and subsequent development occurs through interactions with the external environment and feeding [18]. Within the first 2-3 years, the infant's microbiota undergoes rapid changes and starts resembling that of an adult, influenced by factors like delivery method (vaginal birth or cesarean section), nutrient source (breast milk or formula), geographical location, and exposure to antibiotics[18-24]. This phase is considered vulnerable because disturbances during this period may have significant effects on development [25-27] and future disease susceptibility [26-28]. The microbiota is largely constant during development, adolescence, and maturity. However, certain changes are thought to

happen throughout later life. Understanding the normal microbiota of older people is significant since several neurological disorders are common in the elderly [29].

The diet plays a crucial role in age-related changes in the elderly microbiota. Inadequate dietary intake may lead to a reduction in microbial diversity, which has been associated with inflammation in older individuals, commonly referred to as "inflammaging"[30,31]. Diet's influence on the microbiota is significant throughout all stages of life and can be a confounding factor in studies related to gut microbiota and various diseases [32]. The overall characteristics of the diet, including total calorie intake and whether it is primarily based on highly processed foods or rich in vegetables and fruits[33-35], greatly impact the composition of the microbiota. Additionally, specific dietary elements like carbohydrates [36], proteins [37], fats [38], fiber [39-41], and vitamins[42] also play a role in shaping the microbiota. Due to their typical age group, patients with neurodegenerative diseases often have other physical co-existing conditions. Consequently, they may be prescribed medications that can alter the composition of the gut microbiota, including antibiotics [43,44], proton pump inhibitors[45,46], and metformin[47]. Other prescription and over-the-counter drugs may also have an impact on gut bacterial communities.

The role of the gut microbiota in upholding overall balance and health is constantly being revealed. For the gastrointestinal system and the entire body to function properly, the microbiota must be intact and healthy. The microbiota has roles that are well understood, including supporting the growth and maturation of the mucosal immune system [48,49], maintaining the integrity of the gut barrier (which is thought to be important in some neurological diseases)[50], affecting gut neuromuscular functions[51-53], and carrying out crucial metabolic functions[54,55]. Some of these metabolic processes might produce molecules that affect how the brain operates.

3. Understanding the Gut-Brain Connection: Mechanisms and Pathways

The "gut-microbiota-brain axis" refers to a network connecting different biological systems, enabling two-way communication between gut bacteria and the brain. This communication is crucial for maintaining balance in the gastrointestinal, central nervous, and microbial systems of animals [56,57]. The pathways for communication involve direct and indirect signaling through chemical transmitters, neuronal pathways, and the immune system. Multiple mechanisms and pathways likely work together to influence disease development, but further

research is required to fully comprehend these mechanisms. Throughout the Review, we delve into the complexity of these connections and highlight areas where different communication methods intersect in the context of human disease.

3.1 Chemical signaling between the gut and the brain:

The gut microbiota plays a role in maintaining balance and influencing behavior in its host animal through chemical communication with the nervous system. This communication encompasses both indirect and direct signaling, for example, short-chain fatty acids (SCFAs), which are produced by gut microorganisms during the fermentation of dietary fiber, can directly affect the central nervous system (CNS) in preclinical models by regulating neuroplasticity, epigenetic processes, gene expression, and the immune system [58]. Indirectly, the microbiota can impact the nervous system and behavior by influencing the neuroendocrine system. This can be observed in how gut microorganisms regulate appetite and feeding behaviors by affecting the production of endocrine signals from enteroendocrine cells (EECs) in the gut epithelium, including the hormone glucagon-like peptide 1 (GLP1) [59,60]. Mice that do not have a natural microbiota, known as germ-free (GF) mice, consume less food compared to regular mice with a normal microbiota [61]. Both GF mice and mice treated with antibiotics produce lower levels of GLP1 (glucagon-like peptide 1) compared to mice with a conventional gut microbiota [62]. This indicates that the gut microbiota can influence this behavior that is regulated by hormones. The bacterial metabolite indole, which increases colonic vagal afferent activity in rats, can influence the release of GLP1 by colonic enteroendocrine L cells. [63]. Furthermore, in model systems, the gut microbiota also regulates the levels of neurotransmitters. This suggests that microorganisms may serve as agents influencing the classical signaling molecules employed by the nervous system [64-67]. Gut microbes can synthesize neurotransmitters on their own and can stimulate the creation of neurotransmitters in their animal hosts. For instance, various microbes, including Bacteroides, Bifidobacterium, Parabacteroides, and Escherichia spp., are known to create the neurotransmitter -aminobutyric acid (GABA) [64].

Bacteria play a pivotal role in the synthesis of the neurotransmitter serotonin, which is also referred to as 5-hydroxytryptamine or 5-HT. The production and secretion of 5-HT by enteroendocrine cells (EECs) are influenced by microbial metabolites like indole, SCFAs, secondary bile acids, α-tocopherol, p-aminobenzoate, and tyramine[66,68]. Both germ-free (GF) mice and mice treated with antibiotics have lower 5-HT biosynthesis, but this effect can

be reversed by introducing spore-forming bacteria that increase tryptophan metabolism by enterochromaffin cells [66]. Notably, when spore-forming bacteria sourced from a healthy human gut microbiota are transplanted into germ-free (GF) mice, they produce similar effects. This indicates that the influence of the gut microbiota on tryptophan metabolism is a shared characteristic throughout the evolution of mammals [66].

Most of the 5-HT is produced in the gut, and changes in gut levels do not directly affect brain 5-HT levels because 5-HT cannot cross the blood-brain barrier (BBB) [66]. However, GF mice have lower concentrations of 5-HT and its precursor tryptophan in the hippocampus, indicating that gut microbiota may influence 5-HT signaling pathways in the central nervous system (CNS). The exact mechanisms linking the gut microbiota to 5-HT production in the brain are still unknown. It is challenging to determine how much microbial metabolism directly influences CNS activity due to a lack of clear understanding of the transport rates of many microbial metabolites into the brain. As a result, distinguishing the specific influence of microbial metabolites on central nervous system (CNS) function from other communication pathways, such as immune or neuronal pathways, poses challenges in vivo experiments [69].

In future research, a better understanding of the impact of chemical signaling on gut-brain connections can be achieved by integrating metabolomic and metagenomic profiles with functional behavioral outcomes. This approach will provide more clarity on the role of chemical signaling in the interactions between the gut and the brain.

3.2 Neuronal pathways for gut–brain interactions:

Neuronal pathways create a direct link between the gut and the brain, with the vagus nerve being a major pathway. This nerve extends from the brainstem and innervates both the gut and the enteric nervous system (ENS). The gut microbiota plays a role in the development and function of the ENS, although this area of research is still relatively unexplored.

The afferent branch of the vagus nerve is essential for connecting the gastrointestinal (GI) tract to the brain's nucleus of the solitary tract and higher emotion-regulating networks in mammals [70]. While it may not directly interact with the gut microbiota, evidence suggests that the vagus nerve can sense microbial signals in the form of bacterial metabolites [71]. The gut microbiota can influence the vagus nerve by affecting gut epithelium cells such as enteroendocrine and enterochromaffin cells (ECCs), which impact various physiological functions in the intestines [71].

Studies in mice that underwent vagotomy (surgical cutting of the vagus nerve) indicates that the vagus nerve may be involved in communication between the central nervous system (CNS) and the gut microbiota, potentially affecting mood and neurobehavioral disorders. For instance, vagotomy in mice prevented certain gut bacteria like *Lactobacillus* and *Bifidobacterium* species from exerting mood-modifying effects [72-74].

Recent research suggests a bidirectional communication system between diet, the gut microbiome, ECCs, and the vagus nerve. ECCs contain a significant amount of the body's serotonin (5-HT), and the synthesis and release of 5-HT in ECCs are influenced by microbial metabolites such as SCFAs and 2BAs produced by spore-forming Clostridiales [75,76]. These microbial metabolites have more significant effects on ECCs when there is higher dietary tryptophan availability. ECCs also communicate with afferent nerve fibers through synaptic connections [77]. On the other hand, the autonomic nervous system (ANS) can activate ECCs to release 5-HT into the gut, impacting gut microbial function, and being taken up by serotonin transporter-like mechanisms [78].

In conclusion, there exists a complex and interconnected system involving the gut microbiota, the vagus nerve, and gut epithelium cells, which influence various physiological and neurological processes in the gut-brain axis. Further research is required to fully comprehend the mechanisms and implications of this communication system.

3.3 Gut microbiota–brain signaling through the immune system:

A properly functioning immune system in the gut is essential to maintain a delicate balance between accepting beneficial microorganisms and protecting the body from harmful ones. Immunity also plays a critical role in facilitating communication among the gut microbiota, the enteric nervous system (ENS), and the brain. Toll-like receptors (TLRs) and peptidoglycans (PGNs) act as sensors for microbial components [79,80], initiating the immune response to microbes.

Maintaining an intact gut barrier is crucial to prevent inappropriate activation of immune cells and systemic immune responses. Bacteria can release immune-stimulating substances into the bloodstream, allowing them to reach the brain. TLRs have been found in the brain, especially in microglia, and have been studied about diseases like Alzheimer's[81], Parkinson's[82], visceral pain[83], and depression[84]. Manipulating the gut microbiota, as seen in germ-free (GF) or antibiotic-treated mice, affects the expression of receptors detecting

PGNs in the brain, suggesting that the microbiota influences gene expression in the brain and behavior [84].

Changes in the gut microbiome due to dietary shifts can compromise the protective mucus layer, enabling luminal microbes to interact with dendritic cells and activate them, whether they are harmful pathogens or beneficial commensals. This local immune activation can increase the permeability of epithelial tight junctions, further compromising the intestinal barrier. Such immune activation, triggered by diet, can lead to the release of immune mediators into the systemic circulation, referred to as metabolic endotoxemia. This, in turn, triggers immune responses in various organs, including the brain[85]. Low-grade immune activation has been linked to specific types of depression and neurodegenerative disorders like Alzheimer's and Parkinson's disease.

To gain a comprehensive understanding of the implications of immune signaling in health and disease, more research is needed, particularly regarding the gut-brain axis. The intricate interactions between the gut microbiota, the immune system, and the brain play a vital role in maintaining overall health and well-being.

4. The microbiota-gut-brain axis and brain disorders

It is clear that an unstable gut microbiota in either early childhood or old age significantly increases the likelihood of brain dysfunction. However, the precise relationship between these observations is not fully understood. Discovering the mechanisms and pathways that link the microbiota to brain function could provide valuable new insights into individual variations and potentially lead to the development of innovative treatments for neurodevelopmental and neurodegenerative disorders such as autism and Parkinson's disease.

4.1 Alzheimer's disease and dementia

Alzheimer's disease is a progressive form of dementia that affects the brain, leading to memory and thinking difficulties, ultimately impacting daily activities. The disease is characterized by the presence of amyloid plaque and hyperphosphorylation of tau protein in the brain. Alzheimer's can be classified as familial (a small percentage of cases) or sporadic (the majority of cases). In the case of sporadic Alzheimer's disease, infections may play a role in the development of its pathology. There have been studies suggesting that various infectious agents, such as viruses, parasites, bacteria, and fungi, could be contributing factors

to the development of Alzheimer's disease [86,87]. Interestingly, this idea is not new, as Aloysius Alzheimer himself proposed the involvement of microorganisms in the disease's progression [88,89].

Recent research has shown promising results with probiotics, which are beneficial microorganisms, in the context of Alzheimer's disease. For instance, a probiotic combination containing B. *longum* and *Lactobacillus spp.* improved cognitive function and metabolic status in Alzheimer's patients [90]. Additionally, co-supplementation of probiotics and selenium for 12 weeks showed improved cognitive function and reduced inflammation and oxidative stress markers compared to selenium-only or placebo groups in Alzheimer's patients. In another study, probiotic supplementation in Alzheimer's patients influenced the composition of gut bacteria and the metabolism of tryptophan in the serum. Following the treatment, these patients exhibited lower intestinal permeability and higher levels of *Faecalibacterium prausnitzii*, a microorganism that produces beneficial short-chain fatty acids (SCFAs), compared to the control group [91].

These findings suggest that probiotics may hold potential to improve cognitive function not only in Alzheimer's patients but also in healthy populations.

4.2 Anxiety

The connection between anxiety and the microbiota-gut-brain axis has mostly been studied in animals (preclinical studies). Some studies administering probiotics have shown improvements in certain anxiety measures. However, a meta-analysis of randomized controlled trials that looked at the effectiveness of probiotics in treating anxiety did not find any significant difference between probiotics and placebo in reducing anxiety symptoms [92].

In a study involving stressed adults, a 12-week treatment with *Lactobacillus plantarum*, a type of probiotic, led to a reduction in stress and anxiety symptoms, as well as overall scores on the Depression Anxiety Stress Scales-42. The individuals who received probiotics also had lower levels of the stress hormone cortisol and pro-inflammatory cytokines in their blood compared to those who received a placebo. Interestingly, in healthy adults over the age of 30, the L. *plantarum* treatment resulted in improved cognitive and memory functions, such as better attention, emotional cognition, and associated learning, compared to the placebo group and a group of young adults (under 30 years old).

The administration of probiotics seems to have an impact on the serotonin pathway, which is involved in regulating mood. The levels of certain enzymes involved in serotonin production and breakdown, such as dopamine b-hydroxylase, tyrosine hydroxylase, indoleamine 2,3-dioxygenase, and tryptophan 2,3-dioxygenase, were reduced by probiotics. At the same time, probiotics increased the levels of tryptophan hydroxylase-2 and 5-hydroxytryptamine receptor-6 in the patients' blood [93]. These changes in serotonin-related substances could be linked to the observed improvements in anxiety and cognitive function.

In summary, while much of the evidence supporting the link between anxiety and the microbiota-gut-brain axis comes from animal studies, some human trials with specific probiotics have shown promising results in reducing anxiety and improving cognitive function in stressed and healthy adults. However, a meta-analysis of overall probiotic trials for anxiety did not find consistent positive effects. More research is needed to fully understand the relationship between probiotics, gut health, and mental well-being.

4.3 Autism spectrum disorder

In the United States, there has been a noticeable increase in autism cases over the past few decades. Recent evidence suggests a potential link between the gut microbiota (microorganisms in the digestive system) and autism. The use of the antibiotic vancomycin in children with regressive autism showed some improvement in behavioral issues, indicating a connection with gut health [94]. Individuals with autism often have a higher prevalence of GI disorders, including inflammatory bowel disease [95], which seems to be related to the severity of their symptoms[96].

Maternal infection and inflammation during pregnancy have also been associated with an increased risk of autism in children. Researchers used a mouse model of maternal immune activation (MIA) to investigate the role of the gut microbiota in autism. Offspring from MIA mothers had changes in their gut microbiota, along with increased intestinal permeability, potentially allowing harmful components to enter the bloodstream. This was accompanied by altered levels of certain metabolites, including 4-ethylphenylsulfate (4-EPS), which seemed to influence the gut-brain axis and anxiety-related behaviors.

Notably, beneficial gut bacteria, such as *Bacteroides fragilis*, play a role in maintaining intestinal immune responses [97,98]. When MIA offspring were colonized with a *B. fragilis* strain containing a specific polysaccharide A, their gut barrier function improved, gut

microbiota composition normalized, and 4-EPS levels decreased, leading to improved behavior [99].

These studies highlight how imbalances in the gut microbiome, influenced by maternal immune factors, can lead to changes in offspring, including behavior. Manipulating the gut microbiota may offer new possibilities for therapeutic interventions in autism.

4.4 Parkinson's disease

Parkinson's disease is characterized by the accumulation of alpha-synuclein protein, which affects the enteric nervous system and parasympathetic nerves early on. A study by Scheperjans et al. [100] provided initial evidence linking the gut microbiota to Parkinson's disease. They compared the gut bacteria of Parkinson's patients with healthy individuals and found that *Prevotellaceae* was significantly reduced (by 77.6%) in Parkinson's patients, while *Enterobacteriaceae* was associated with postural instability and gait difficulty [100].

Another study showed that Parkinson's patients experience gut bacteria imbalance (intestinal dysbiosis) and reduced levels of LPS-binding protein, which is involved in combating bacterial endotoxins. High acute levels of endotoxins increase LPS-binding protein, but chronic exposure decreases it [101].

In a placebo-controlled clinical trial, Parkinson's patients received probiotics with beneficial bacteria. After the treatment, patients showed improved Parkinson's disease scores, reduced inflammation (measured by high-sensitivity C-reactive protein), lower oxidative damage, and increased enzymatic defense [102].

Furthermore, a Swedish study suggested that truncal vagotomy, a surgical procedure removing specific nerve fibers, might have a potential protective effect against developing Parkinson's disease, as indicated by a matched cohort study.

In summary, research indicates a connection between the gut microbiota and Parkinson's disease. Modifying gut bacteria and using probiotics show promise as potential therapeutic approaches for managing Parkinson's symptoms and inflammation. Additionally, certain surgical interventions, like truncal vagotomy, may offer protection against developing Parkinson's disease.

4.5 Schizophrenia

A recent study compared the gut microbiome of people with chronic schizophrenia to that of healthy individuals. The results showed differences in the composition, with schizophrenia patients having lower levels of *Proteobacteria*, higher levels of *Anaerococcus*, and lower levels of *Haemophilus*, *Sutterella*, and *Clostridium* compared to healthy controls. Schizophrenia patients also had an increased abundance of *Ruminococcaceae*, which was associated with milder negative symptoms, and higher levels of *Bacteroides* and *Coprococcus sp*., which were linked to more severe depressive symptoms and an increased risk of coronary heart disease, respectively [103].

In a trial involving 60 patients with chronic schizophrenia, treatment with vitamin D and probiotics together showed significant improvements in their Positive and Negative Syndrome Scale scores. It also led to increased antioxidant capacity related to the microbiota-gut-brain axis and reduced levels of malondialdehyde and high sensitivity C-reactive protein compared to the placebo [104].

In an open-label study, all participants with schizophrenia received *Bifidobacterium* breve for 4 weeks, resulting in improvements in anxiety and depressive symptoms [105].

Another placebo-controlled study investigated the effects of probiotics on yeast antibody levels and bowel discomfort in schizophrenia patients. The researchers found that probiotic treatment significantly reduced *Candida albicans* antibodies in men, leading to a normalization of *C. albicans* antibody levels and reduced gut discomfort related to *C. albicans* in many men [106].

Furthermore, mice that received faecal transplants from individuals with schizophrenia exhibited changes in neurotransmitter levels in the hippocampus and displayed behaviors relevant to schizophrenia[106].

Overall, these findings suggest a potential link between the gut microbiome and schizophrenia. Interventions such as probiotics and vitamin D co-supplementation show promise in improving symptoms and antioxidant capacity in schizophrenia patients.

5. The role of probiotics and prebiotics in MGB axis modulation

In recent years, there has been increasing interest in using pre- and probiotics to optimize the gut microbiota and their potential impact on neuropsychiatric disorders, particularly anxiety and stress.

Probiotics are live microorganisms that offer health benefits when taken in adequate amounts. They mainly consist of *Lactobacillus and Bifidobacterium* bacteria. Animal studies have shown the positive effects of probiotics on various diseases and cognitive outcomes [107]. Specific probiotics like *Lactobacillus rhamnosus*, helventicus, and *fermentum* have been found to improve memory impairment in mice[108]. Clinical trials using combinations of *Lactobacillus* subspecies have shown cognitive improvements in Alzheimer's disease patients.

In autism spectrum disorder (ASD), a clinical trial using *Lactobacillus rhamnosus* supplementation indicated a reduced risk of neuropsychiatric disorder development in infants [109]. Prebiotics, which are selectively utilized by host microorganisms for health benefits, can also influence the gut microbiota and the gut-brain axis. Studies with fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) in mice demonstrated antidepressant and anxiolytic effects, while N-Acetylcysteine (NAC) administration in ASD infants reduced repetitive behavior and irritability[110,111].

In conclusion, pre-and probiotics show promise as potential treatment options for neuropsychiatric disorders. However, more research, particularly randomized clinical trials, is necessary to fully understand the underlying mechanisms and determine their true effectiveness, always bearing in mind that correlation does not necessarily imply causation.

6. The role of fecal microbiota transplantation in MGB axis modulation

Fecal microbiota transplantation (FMT) is a treatment recommended for severe *Clostridium difficile* infections and inflammatory bowel diseases, as it can significantly modify the composition of the gut microbiota and potentially correct any imbalances [112]. However, there have been very limited studies conducted to assess FMT's effectiveness in treating neuropsychiatric disorders [113].

In one particular study involving rodents, researchers transferred the gut microbiota from patients with Parkinson's disease into healthy mice through FMT, resulting in the

development of neuroinflammation and motor deficits [114]. Moreover, FMT performed to address constipation in three patients with multiple sclerosis (MS) and in two children with autism spectrum disorder (ASD) showed promising outcomes, leading to significant improvements in neurological and autistic symptoms, respectively [115]. A different study involving children with ASD reported a reduction in behavioral and gastrointestinal symptoms for up to 8 weeks after a treatment involving two weeks of vancomycin followed by FMT [116].

Additionally, there was a case report of a patient with drug-resistant epilepsy and Crohn's disease who underwent FMT for the latter condition and surprisingly achieved a seizure-free condition without the need for antiepileptic medication. Despite the potential benefits of FMT for neuropsychiatric disorders, its clinical application remains a distant possibility.

CONCLUSION

In conclusion, the gut microbiome consists of a diverse and dynamic community of microorganisms residing in the gastrointestinal tract. It plays a vital role in maintaining human health by influencing digestion, metabolism, and immune system regulation. Through the gut-brain axis, a bidirectional communication system, the microbiota can directly impact brain function and behaviour.

The communication pathways involved in this process are intricate, involving chemical transmitters, neuronal pathways, and the immune system. Notably, short-chain fatty acids (SCFAs) produced by gut microorganisms have direct effects on the central nervous system (CNS), while the vagus nerve establishes a direct link between the gut and the brain. Moreover, the immune system plays a crucial role in facilitating communication between the gut microbiota, the enteric nervous system, and the brain.

Recent research suggests that imbalances in the gut microbiota may be associated with various brain disorders, such as Alzheimer's disease, anxiety, autism spectrum disorder, Parkinson's disease, and schizophrenia. Promisingly, probiotics (beneficial microorganisms) and prebiotics (substances that support the growth of beneficial bacteria) offer potential treatment options for these conditions. Additionally, fecal microbiota transplantation (FMT) has shown positive effects in specific neuropsychiatric disorders, though more investigation is needed.

Understanding the interactions between the gut and the brain opens new avenues for potential therapeutic interventions in neuropsychiatric conditions. However, further research is necessary to fully grasp the mechanisms and implications of the gut-brain connection, as well as to determine the true effectiveness of interventions like probiotics, prebiotics, and FMT in managing brain-related disorders. As our knowledge of the gut-brain axis advances, it holds the promise of innovative approaches to enhance both gut and brain health in the future.

REFERENCES

1. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell research. 2020 Jun;30(6):492-506.
2. Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. The Journal of Clinical Investigation. 2019 Oct 1;129(10):4050-7.
3. Collins J, Borojevic R, Verdu EF, Huizinga JD, Ratcliffe EM. Intestinal microbiota influence the early postnatal development of the enteric nervous system. Neurogastroenterology & Motility. 2014 Jan;26(1):98-107.
4. de la Cuesta-Zuluaga J, Kelley ST, Chen Y, Escobar JS, Mueller NT, Ley RE, et al. Age- and sex-dependent patterns of gut microbial diversity in human adults. mSystems. 2019;4(4). doi:10.1128/msystems.00261-19
5. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559-63.
6. Vich Vila A, Collij V, Sanna S, Sinha T, Imhann F, Bourgonje AR, Mujagic Z, Jonkers DM, Masclee AA, Fu J, Kurilshikov A. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. Nature communications. 2020 Jan 17;11(1):362.
7. Sender R, Fuchs S, Milo R. Are we vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell. 2016 Jan 28;164(3):337-40.
8. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. science. 2005 Jun 10;308(5728):1635-8.
9. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE. The microbiota-gut-brain axis. Physiological reviews. 2019 Aug 28.
10. Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. Cellular and molecular gastroenterology and hepatology. 2018 Jan 1;6(2):133-48.
11. Yarandi SS, Peterson DA, Treisman GJ, Moran TH, Pasricha PJ. Modulatory effects of gut microbiota on the central nervous system: how gut could play a role in neuropsychiatric health and diseases. Journal of neurogastroenterology and motility. 2016 Apr;22(2):201.
12. Theoharides TC, Kavalioti M, Tsilioni I. Mast cells, stress, fear and an autism spectrum disorder. International journal of molecular sciences. 2019 Jul 24;20(15):3611.
13. Willner P, Scheel-Krüger J, Belzung C. The neurobiology of depression and antidepressant action. Neuroscience & biobehavioral reviews. 2013 Dec 1;37(10):2331-71.
14. Rocha EM, De Miranda B, Sanders LH. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiology of disease. 2018 Jan 1; 109:249-57.
15. Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. Cellular and molecular gastroenterology and hepatology. 2018 Jan 1;6(2):133-48.
16. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M. Erratum: Enterotypes of the human gut microbiome (Nature (2011) 473 (174-180)). Nature. 2011 Jun 30;474(7353):666.
17. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8.

18. Neu J. The microbiome during pregnancy and early postnatal life. InSeminars in fetal and neonatal medicine 2016 Dec 1 (Vol. 21, No. 6, pp. 373-379). WB Saunders.
19. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, Björkstén B, Engstrand L, Andersson AF. Decreased gut microbiota diversity, delayed Bacteroidetes colonization and reduced Th1 responses in infants delivered by caesarean section. Gut. 2014 Apr 1;63(4):559-66.
20. Dogra S, Sakwinska O, Soh SE, Ngom-Bru C, Brück WM, Berger B, Brüssow H, Lee YS, Yap F, Chong YS, Godfrey KM. Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity. MBio. 2015 Feb 27;6(1):10-128.
21. Cong X, Xu W, Janton S, Henderson WA, Matson A, McGrath JM, Maas K, Graf J. Gut microbiome developmental patterns in early life of preterm infants: impacts of feeding and gender. PloS one. 2016 Apr 25;11(4):e0152751.
22. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, Khan MT. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell host & microbe. 2015 May 13;17(5):690-703.
23. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC. The human gut microbiome is viewed across age and geography. nature. 2012 Jun 14;486(7402):222-7.
24. Vangay P, Ward T, Gerber JS, Knights D. Antibiotics, pediatric dysbiosis, and disease. Cell host & microbe. 2015 May 13;17(5):553-64.
25. Heijtz RD. Fetal, neonatal, and infant microbiome: Perturbations and subsequent effects on brain development and behavior. InSeminars in Fetal and Neonatal Medicine 2016 Dec 1 (Vol. 21, No. 6, pp. 410-417). WB Saunders.
26. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. Cell. 2016 Nov 3;167(4):915-32.
27. Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, aging and neurodegeneration. The Journal of physiology. 2017 Jan 15;595(2):489-503.
28. Zeissig S, Blumberg RS. Life at the beginning: perturbation of the microbiota by antibiotics in early life and its role in health and disease. Nature immunology. 2014 Apr;15(4):307-10.
29. Kumar M, Babaei P, Ji B, Nielsen J. Human gut microbiota and healthy aging: recent developments and future prospective. Nutrition and Healthy aging. 2016 Jan 1;4(1):3-16.
30. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris H, Coakley M, Lakshminarayanan B, O'sullivan O, Fitzgerald GF. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012 Aug;488(7410):178-84.
31. Odamaki T, Kato K, Sugahara H, Hashikura N, Takahashi S, Xiao JZ, Abe F, Osawa R. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC microbiology. 2016 Dec;16(1):1-2.
32. Shanahan F, van Sinderen D, O'Toole PW, Stanton C. Feeding the microbiota: transducer of nutrient signals for the host. Gut. 2017 Sep 1;66(9):1709-17.
33. Doré J, Blottière H. The influence of diet on the gut microbiota and its consequences for health. Current opinion in biotechnology. 2015 Apr 1;32:195-9.
34. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, Kau AL, Rich SS, Concannon P, Mychaleckyj JC, Liu J. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science. 2013 Feb 1;339(6119):548-54.
35. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, Benezra A, DeStefano J, Meier MF, Muegge BD, Barratt MJ. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. 2014 Jun 19;510(7505):417-21.
36. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. Cell metabolism. 2014 Nov 4;20(5):779-86.
37. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB, Wood-Martin R, Kerins DM. Exercise and associated dietary extremes impact on gut microbial diversity. Gut. 2014 Dec 1;63(12):1913-20.

38. Hildebrandt MA, Hoffmann C, Sherrill–Mix SA, Keilbaugh SA, Hamady M, Chen YY, Knight R, Ahima RS, Bushman F, Wu GD. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009 Nov 1;137(5):1716-24.
39. Heinritz SN, Weiss E, Eklund M, Aumiller T, Louis S, Rings A, Messner S, Camarinha-Silva A, Seifert J, Bischoff SC, Mosenthin R. Intestinal microbiota and microbial metabolites are changed in a pig model fed a high-fat/low-fiber or a low-fat/high-fiber diet. PloS one. 2016 Apr 21; 11(4):e0154329.
40. Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, Hallen A, Martens E, Björck I, Bäckhed F. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of Prevotella. Cell metabolism. 2015 Dec 1;22(6):971-82.
41. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016 Jan 14;529(7585):212-5.
42. Degnan PH, Taga ME, Goodman AL. Vitamin B12 as a modulator of gut microbial ecology. Cell metabolism. 2014 Nov 4;20(5):769-78.
43. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. The Journal of Clinical Investigation. 2014 Oct 1;124(10):4212-8.
44. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. Science. 2016 Apr 29;352(6285):544-5.
45. Freedberg DE, Toussaint NC, Chen SP, Ratner AJ, Whittier S, Wang TC, Wang HH, Abrams JA. Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: a crossover trial. Gastroenterology. 2015 Oct 1;149(4):883-5.
46. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT, Spector TD. Proton pump inhibitors alter the composition of the gut microbiota. Gut. 2016 May 1;65(5):749-56.
47. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Krogh Pedersen H, Arumugam M. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015 Dec 10;528(7581):262-6.
48. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome, and the immune system. Nature. 2011 Jun 16;474(7351):327-36.
49. Surana NK, Kasper DL. Deciphering the tête-à-tête between the microbiota and the immune system. The Journal of clinical investigation. 2014 Oct 1;124(10):4197-203.
50. Wells JM, Brummer RJ, Derrien M, MacDonald TT, Troost F, Cani PD, Theodorou V, Dekker J, Méheust A, De Vos WM, Mercenier A. Homeostasis of the gut barrier and potential biomarkers. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2017 Mar 1;312(3):G171-93.
51. Dey N, Wagner VE, Blanton LV, Cheng J, Fontana L, Haque R, Ahmed T, Gordon JI. Regulators of gut motility revealed by a gnotobiotic model of diet-microbiome interactions related to travel. Cell. 2015 Sep 24;163(1):95-107.
52. Kabouridis PS, Lasrado R, McCallum S, Chng SH, Snippert HJ, Clevers H, Pettersson S, Pachnis V. The gut microbiota keeps enteric glial cells on the move; prospective roles of the gut epithelium and immune system. Gut Microbes. 2015 Nov 2;6(6):398-403.
53. Savidge TC. Epigenetic regulation of enteric neurotransmission by gut bacteria. Frontiers in cellular neuroscience. 2016 Jan 8;9:503.
54. Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance, and obesity. The Journal of Physiology. 2009 Sep 1;587(17):4153-8.
55. Carmody RN, Turnbaugh PJ. Host-microbial interactions in the metabolism of therapeutic and diet-derived xenobiotics. The Journal of Clinical Investigation. 2014 Oct 1;124(10):4173-81.
56. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE. The microbiota-gut-brain axis. Physiological reviews. 2019 Aug 28.
57. Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. Cellular and molecular gastroenterology and hepatology. 2018 Jan 1;6(2):133-48.
58. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota–gut–brain communication. Nature reviews Gastroenterology & hepatology. 2019 Aug;16(8):461-78.

59. Ghatei MA, Ratcliffe B, Bloom SR, Goodlad RA. Fermentable dietary fibre, intestinal microflora and plasma hormones in the rat. Clinical Science. 1997 Aug 1;93(2):109-12.
60. Aresti Sanz J, El Aidy S. Microbiota and gut neuropeptides: a dual action of antimicrobial activity and neuroimmune response. Psychopharmacology. 2019 May 1;236(5):1597-609.
61. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. Proceedings of the national academy of sciences. 2004 Nov 2;101(44):15718-23.
62. Wichmann A, Allahyar A, Greiner TU, Plovier H, Lundén GÖ, Larsson T, Drucker DJ, Delzenne NM, Cani PD, Bäckhed F. Microbial modulation of energy availability in the colon regulates intestinal transit. Cell host & microbe. 2013 Nov 13;14(5):582-90.
63. Buckley MM, O'Brien R, Brosnan E, Ross RP, Stanton C, Buckley JM, O'Malley D. Glucagon-like peptide-1 secreting L-cells coupled to sensory nerves translate microbial signals to the host rat nervous system. Frontiers in Cellular Neuroscience. 2020 Apr 30;14:95.
64. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, McDonald D, Dietrich D, Ramadhar TR, Lekbua A, Mroue N. GABA-modulating bacteria of the human gut microbiota. Nature Microbiology. 2019 Mar;4(3):396-403.
65. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. Journal of Applied Microbiology. 2012 Aug 1;113(2):411-7.
66. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015 Apr 9;161(2):264-76.
67. Poutahidis T, Kearney SM, Levkovich T, Qi P, Varian BJ, Lakritz JR, Ibrahim YM, Chatzigiagkos A, Alm EJ, Erdman SE. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. PloS one. 2013 Oct 30;8(10):e78898.
68. Morris G, Berk M, Carvalho A, Caso JR, Sanz Y, Walder K, Maes M. The role of the microbial metabolites including tryptophan catabolites and short-chain fatty acids in the pathophysiology of immune-inflammatory and neuroimmune disease. Molecular neurobiology. 2017 Aug;54:4432-51.
69. Muller PA, Schneeberger M, Matheis F, Wang P, Kerner Z, Ilanges A, Pellegrino K, Del Mármol J, Castro TB, Furuichi M, Perkins M. Microbiota modulate sympathetic neurons via a gut–brain circuit. Nature. 2020 Jul 16;583(7816):441-6.
70. Han W, Tellez LA, Perkins MH, Perez IO, Qu T, Ferreira J, Ferreira TL, Quinn D, Liu ZW, Gao XB, Kaelberer MM. A neural circuit for gut-induced reward. Cell. 2018 Oct 18;175(3):665-78.
71. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Frontiers in neuroscience. 2018 Feb 7;12:49.
72. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell. 2016 Jun 16;165(7):1762-75.
73. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences. 2011 Sep 20;108(38):16050-5.
74. Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, Deng Y, Blennerhassett PA, Fahnestock M, Moine D, Berger B. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut–brain communication. Neurogastroenterology & Motility. 2011 Dec;23(12):1132-9.
75. Reigstad CS, Salmonson CE, Rainey III JF, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G, Kashyap PC. Gut microbes promote colonic serotonin production through the effect of short-chain fatty acids on enterochromaffin cells. The FASEB Journal. 2015 Apr;29(4):1395.
76. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015 Apr 9;161(2):264-76.
77. Bohórquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, Calakos N, Wang F, Liddle RA. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. The Journal of Clinical Investigation. 2015 Feb 2;125(2):782-6.

78. Sgritta M, Dooling SW, Buffington SA, Momin EN, Francis MB, Britton RA, Costa-Mattioli M. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. Neuron. 2019 Jan 16;101(2):246-59.
79. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell. 2004 Jul 23;118(2):229-41.
80. Chu H, Mazmanian SK. Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nature immunology. 2013 Jul;14(7):668-75.
81. Lin C, Zhao S, Zhu Y, Fan Z, Wang J, Zhang B, Chen Y. Microbiota-gut-brain axis and toll-like receptors in Alzheimer's disease. Computational and structural biotechnology journal. 2019 Jan 1;17:1309-17.
82. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, Voigt RM, Naqib A, Green SJ, Kordower JH, Shannon KM. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut. 2019 May 1;68(5):829-43.
83. Tramullas M, Finger BC, Moloney RD, Golubeva AV, Moloney G, Dinan TG, Cryan JF. Toll-like receptor 4 regulates chronic stress-induced visceral pain in mice. Biological psychiatry. 2014 Aug 15;76(4):340-8.
84. Arentsen T, Qian Y, Gkotzis S, Femenia T, Wang T, Udekwu K, Forssberg H, Diaz Heijtz R. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. Molecular psychiatry. 2017 Feb;22(2):257-66.
85. André P, Laugerette F, Féart C. Metabolic endotoxemia: a potential underlying mechanism of the relationship between dietary fat intake and risk for cognitive impairments in humans?. Nutrients. 2019 Aug 13;11(8):1887.
86. Torres L, Robinson SA, Kim DG, Yan A, Cleland TA, Bynoe MS. Toxoplasma gondii alters NMDAR signaling and induces signs of Alzheimer's disease in wild-type, C57BL/6 mice. Journal of Neuroinflammation. 2018 Dec;15:1-9.
87. Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, Moir RD. Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Science translational medicine. 2016 May 25;8(340):340ra72-.
88. Hill JM, Clement C, Pogue AI, Bhattacharjee S, Zhao Y, Lukiw WJ. Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). Frontiers in aging neuroscience. 2014:127.
89. Giridharan VV, Masud F, Petronilho F, Dal-Pizzol F, Barichello T. Infection-induced systemic inflammation is a potential driver of Alzheimer's disease progression. Frontiers in aging neuroscience. 2019 May 28;11: 122.
90. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Frontiers in aging neuroscience. 2016 Nov 10;8: 256.
91. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with Alzheimer's dementia-an explorative intervention study. Current Alzheimer Research. 2018 Nov 1;15(12):1106-13.
92. Liu B, He Y, Wang MI, Liu J, Ju Y, Zhang Y, Liu T, Li L, Li Q. Efficacy of probiotics on anxiety—A meta-analysis of randomized controlled trials. Depression and anxiety. 2018 Oct;35(10):935-45.
93. Chong HX, Yusoff NA, Hor YY, Lew LC, Jaafar MH, Choi SB, Yusoff MS, Wahid N, Abdullah MF, Zakaria N, Ong KL. Lactobacillus plantarum DR7 alleviates stress and anxiety in adults: a randomised, double-blind, placebo-controlled study. Beneficial microbes. 2019 Apr 19;10(4):355-73.
94. Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Väisänen ML, Nelson MN, Wexler HM. Short-term benefit from oral vancomycin treatment of regressive-onset autism. Journal of Child Neurology. 2000 Jul;15(7):429-35.
95. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, Bickel J, Wattanasin N, Spence S, Murphy S, Churchill S. The co-morbidity burden of children and young adults with autism spectrum disorders. PloS one. 2012 Apr 12;7(4):e33224.
96. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity. BMC gastroenterology. 2011 Dec;11(1):1-3.
97. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proceedings of the National Academy of Sciences. 2010 Jul 6;107(27):12204-9.

98. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature. 2008 May 29;453(7195):620-5.
99. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH. Microbiota modulates behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013 Dec 19;155(7):1451-63.
100.Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E. Gut microbiota are related to Parkinson's disease and clinical phenotype. Movement Disorders. 2015 Mar;30(3):350-8.
101.Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, Shibata A, Fujisawa Y, Minato T, Okamoto A, Ohno K. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's disease. PloS one. 2015 Nov 5;10(11):e0142164.
102.Tamtaji OR, Taghizadeh M, Kakhaki RD, Kouchaki E, Bahmani F, Borzabadi S, Oryan S, Mafi A, Asemi Z. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clinical Nutrition. 2019 Jun 1;38(3):1031-5.
103.Nguyen TT, Kosciolek T, Maldonado Y, Daly RE, Martin AS, McDonald D, Knight R, Jeste DV. Differences in gut microbiome composition between persons with chronic schizophrenia and healthy comparison subjects. Schizophrenia research. 2019 Feb 1;204:23-9.
104.Ghaderi A, Banafshe HR, Mirhosseini N, Moradi M, Karimi MA, Mehrzad F, Bahmani F, Asemi Z. Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. BMC psychiatry. 2019 Dec;19(1):1-0.
105.Okubo R, Koga M, Katsumata N, Odamaki T, Matsuyama S, Oka M, Narita H, Hashimoto N, Kusumi I, Xiao J, Matsuoka YJ. Effect of bifidobacterium breve A-1 on anxiety and depressive symptoms in schizophrenia: A proof-of-concept study. Journal of Affective Disorders. 2019 Feb 15;245:377-85.
106.Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, Liu Y, Cheng K, Zhou C, Wang H, Zhou X. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Science advances. 2019 Feb 6;5(2):eaau8317.
107.Liu X, Cao S, Zhang X. Modulation of gut microbiota–brain axis by probiotics, prebiotics, and diet. Journal of agricultural and food chemistry. 2015 Sep 16;63(36):7885-95.
108.Gareau MG, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalizes corticosterone release and ameliorates colonic dysfunction induced by maternal separation. Gut. 2007 Nov 1;56(11):1522-8.
109.Pärtty A, Kalliomäki M, Wacklin P, Salminen S, Isolauri E. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatric research. 2015 Jun;77(6):823-8.
110.Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, Stanton C, Dinan TG, Cryan JF. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biological psychiatry. 2017 Oct 1;82(7):472-87.
111.Ghanizadeh A, Moghimi-Sarani E. A randomized double-blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. BMC psychiatry. 2013 Dec;13:1-7.
112.Borody TJ, Campbell J. Fecal microbiota transplantation. Gastroenterology Clinics of North America. 2012;41(4):781–803. doi:10.1016/j.gtc.2012.08.008
113.Xu MQ, Cao HL, Wang WQ, Wang S, Cao XC, Yan F, Wang BM. Fecal microbiota transplantation broadening its application beyond intestinal disorders. World journal of gastroenterology: WJG. 2015 Jan 1;21(1):102.
114.Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF. Gut microbiota regulates motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016 Dec 1;167(6):1469-80.
115.Borody TJ, Brandt LJ, Paramsothy S. Therapeutic fecal microbiota transplantation: current status and future developments. Current opinion in gastroenterology. 2014 Jan;30(1):97.
116.Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017 Dec;5(1):1-6.