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Review Article

The Role of Gut Microbiome and Dysbiosis in Common Psychological, Neurological, and Behavioral Disorders

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Abstract

According to psychobiotic research expansion, the gut microbiome—a colony of more than 1000 species—is connected to brain health and state of mind. Historically, even though a variety of body parts and systems were linked to the nervous system in the nineteenth century, researchers began investigating the gut, especially the stomach, calling it 'the great abdominal brain', 'the great nervous center', and 'the great sensory center'. In addition to the neurons of the enteric nervous system, the gut and brain are connected by the microbiome, which influences the brain by varying mechanisms and contributes to the behavioral state of the individual. A healthy gut flora greatly benefits the host. Dysbiosis or dysbacteriosis occurs when the undesirable bacteria outnumber the desirable bacteria contributed by diet, medications, and stress. Dysbiosis has been linked to several brain disorders, such as autism, schizophrenia, depression, anxiety, attention-deficit hyperactive disorder (ADHD), bipolar disorders, sleep disorders, eating disorders, substance abuse disorders, HIV infection, and neurological disorders (Alzheimer's disease and Parkinson's disease). Gut bacteria interact with the brain in various ways, including neuroendocrine, immunological, and metabolic pathways. This review discusses how dysbiosis affects brain-related disorders. This review also describes the pathogenic microbes that predominated the gut microbiota over other health-giving microbes, and the mechanism underlying the pathogenesis of brain disorders arising from dysbiosis.

Keywords: *AIDS; Antibiotics; Anxiety; Bacteria; Environmental Factors; Firmicutes; Great Abdominal Brain; Intestinal Flora; Lactobacilli; Pathobionts; Probiotics; Stress*

Abbreviations

AD: Alzheimer Disease; ADHD: Attention-Deficit Hyperactivity Disorder; AIDS: Acquired Immunodeficiency Syndrome; AN: Anorexia Nervosa; ASD: Autism Spectrum Disorder; BBB: Blood-Brain Barrier; CNS: Central Nervous System; ENS: Enteric Nervous System; GI: Gastrointestinal Tract; HPA: Hypothalamic-Pituitary-Adrenal Axis; IBD: Inflammatory Bowel Disease; LPS: Liposaccharide; MDD: Major Depressive Disorder; PD: Parkinson Disease; PTSD: Posttraumatic Stress Disorder; SCFA: Short-Chain Fatty Acid; SUD: Substance Abuse Disorder

Introduction

Gut-brain association: the history

Over a century ago, the state of the human gut was believed to influence the state of the human mind. In the late nineteenth and early twentieth centuries, scientists thought that waste accumulation in the colon caused the body to produce toxins that led to infections, resulting in depression, anxiety, and psychoses. The gut and mind have long been known to have an intimate relationship.

Marie François Xavier Bichat, a French anatomist of the eighteenth century, pointed out the gut-brain connection for the first time. Robert Whytt coined the term 'nervous sympathy' in 1765 to describe how visceral organs can be linked [1]. The gut is abundant in nerve endings that send 'nervous energy' through the body. As such, the gut—especially the stomach—became an essential research topic for its apparent effect on emotional and physical well-being [2]. Based on this theory, the researchers described the stomach as 'the great brain of the body' and the 'sensorium of organic life'.

John Abernethy, a leading anatomy teacher at St. Bartholomew's Hospital in London, was passionate about stomach research. Throughout his career, he tirelessly campaigned for a broader recognition of the importance of the stomach and the distressing consequences of 'gastric sympathy'. In his book, *The Abernethian Code of Health and Longevity*, published in 1829, Abernethy traced all diseases and illnesses back to 'gastric derangement'. By suggesting a close relationship between the gut and mind through the nervous system, he explained why emotional conditions, such as excessive worry, reduce appetite by affecting gut health. Similarly, weakened digestion can cause low spirits, restlessness, sleep disorders, and fatigue. He also emphasized that humans need to eat simple, natural foods rather than refined, unnatural, and often adulterated foods [3].

In the early twentieth century, a new generation of psychologists, physiologists, psychoanalysts, and physicians asserted that emotional states must be considered when diagnosing and treating gastric disorders—and that digestive disorders often have psychic roots, and conditions, such as ulcers, may have psychological causes due to the dynamic interrelation between the mind and body physiology [4,5].

Gut bacteria (the microbiome) have been reported to have a significant effect on emotional well-being, which is primarily attributed to the interconnection between the gut, brain, nervous system, and behavior.

Discussion

Gut microbiome

The gut microbiome is a collection of trillions of microorganisms residing in the gut milieu. They include bacteria, viruses, and fungi. The adult human gut contains > 1000 different bacterial species, some pathogenic and others beneficial in maintaining stomach mechanisms and functions [6]. *Bacteroidetes* and *Firmicutes* are the most prominent bacterial groups. The microbe population is referred to as an organ, similar to the liver (1 – 1.5 kg) [7].

The gut microbiota is colonized by microbes that regulate metabolic and immunological functions, resulting in complex microbe and gut microbiota interactions in the host. Also, the gut microbiota performs a critical metabolic function, providing essential nutrients and vitamins and assisting in the extraction of energy and nutrients from food [8]. These functions prevent the overgrowth of potentially pathogenic bacteria in the digestive tract, maintains a homeostatic balance of bacteria, and benefits the host. The complexity of the microbial community, together with its diversity, stability, and resilience, enables the gut microbiota to adapt readily to the gut environment [9].

As a result, the host's intestinal microbiota plays a crucial role in maintaining health. The microflora of the gastrointestinal tract (GI) stimulates the immune system, synthesizes vitamins (B group and K), enhances motility and function of the GI tract, breaks down nutrients, inhibits pathogen populations (colonization resistance), and produces short-chain fatty acids (SCFA) and polyamines [10].

Dysbiosis of the human gut microbiome

Balance of intestinal flora is crucial for maintaining host health. Typically, most bacteria in the intestine are beneficial types of lactic acid-producing, such as *Lactobacilli* and *Bifidobacteria*, and fewer are of less desirable types that produce uncomfortable and annoying gas. Dysbiosis or dysbacteriosis is a condition in which the bacterial balance is disturbed, such that undesirable bacteria outnumber the desirable bacteria.This imbalance exposes the gut to altered gut microbiota.

Dysbiosis results in alterations in bacterial metabolic activities [11]—characterized by a loss of beneficial bacteria, an overabundance of potentially pathogenic bacteria, and attenuation of prevailing bacterial diversity [12].

Causes of dysbiosis

Any significant disruption of intestinal microbiota balance causes dysbiosis. Various factors, such as diet, toxins, drugs, and pathogens, can alter the microbiota.

Diet: The intestinal bacterial balance is greatly affected by the type of diet because different bacteria favor different types of carbohydrates, fibers, and proteins [13]. A dietary change with an increase in proteins, sugars, fats, food additives, or accidental chemical consumption (intake of unwashed fruits, alcoholic beverages, or new medications) can acutely or chronically affect the microbiome.

Antibiotics: Antibiotic use is the most common and significant cause of short- and long-term alterations in the gut flora [14]. The characteristics of the antibiotic, such as the spectrum of antimicrobial activity, pharmacokinetics, dosage, and duration of administration, may influence the gut flora. These agents can adversely affect the microbiome, leading to increased bacteria, such as *Clostridium difficile* or fungi. They may also reduce the production of SCFAs, leading to electrolyte imbalance and diarrhea [15,16].

Stress: Stress can alter the integrity of indigenous microflora for several days. As a result, the intestinal environment becomes less conducive to *Lactobacillus*' survival, adhesion, and replication [17]. For example, according to Lizko (1987), flight journey considered psychological stress, decreased fecal *Bifidobacteria* and *Lactobacillus* in a human study [18]. Also, stress leads to a decreased production of immunoglobulin A, which increases gut colonization with potentially pathogenic microorganisms, such as *Escherichia coli* [18]. Moreover, anger or fear led to a 20–30% rise in the proportion of fecal *Bacteroides fragilis* subsp., returning to normal levels after the situation resolved [19].

Environmental factors: Environmental factors also play a role in gut dysbiosis. Cong and Xu (2016) noted an association with changes in microbiome diversity in the womb, breastfeeding regimens, and hospital environments in infancy [20]. Moreover, insect genomics emphasizes the role of host genetic factors in determining the composition and response of human microbial biofilms.

Dysbiosis, caused by genetic variants that affect microbial recognition and host response, contributes to creating an environment conducive to changes in microbiota [21]. The factors leading to the development of dysbiosis and the consequences of the condition are detailed in Figure 1 [22].

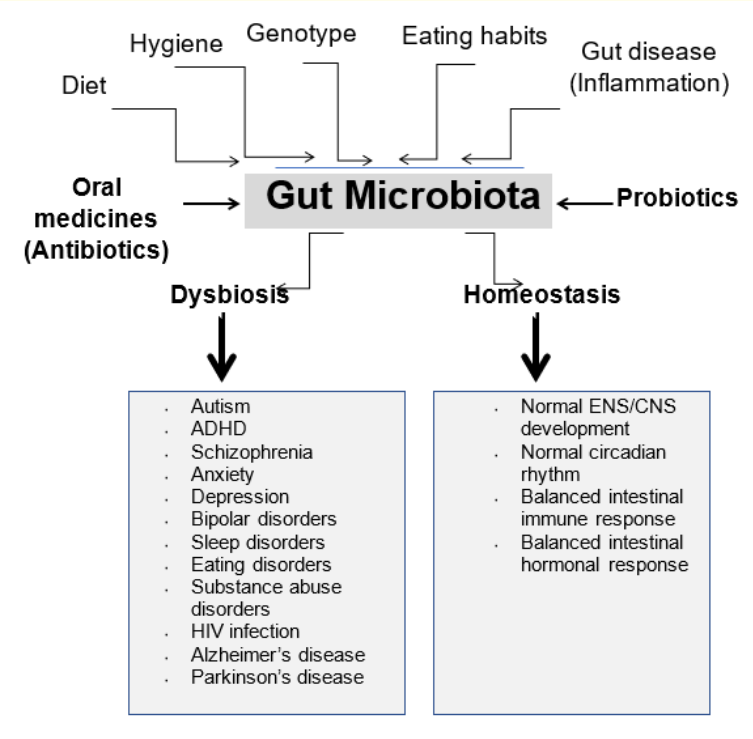

Figure 1: *Internal and external factors affect the gut microbiota, disrupting gut homeostasis (dysbiosis). This dysbiosis can result in psychological and neurological disorders. Adapted from Nibali., et al. (2016) [22].*

Pathophysiological consequences of dysbiosis

Gut dysbiosis, an imbalance in intestinal microorganisms, can develop chronic and degenerative diseases, adversely affecting the host's health. Nibali., *et al*. (2016) noted that dysbiosis has been implicated in inflammatory bowel disease (IBD), obesity, allergic disorders, type 1 diabetes mellitus, autism, obesity, colorectal cancer, and brain disorders in animal and human models [22]. The gut microbiome also strongly interacts with certain drugs, including those prescribed for mental illnesses, and modifies their effects.

Cryan and Dinan (2012) reported that disturbances in the composition and function of certain microbiota constituents had been associated with the outcome of neurological disorders [23]. According to Collins and Bercik (2009), the gut and brain demonstrate bidirectional communication [24].

Autism spectrum disorder (ASD): Increasing evidence suggests the crucial role of commensal bacteria in autism spectrum disorders (ASDs). It remains unclear whether dysbiosis and GI dysfunction are sequelae of the more considerable disorder or directly cause ASD. The first studies investigating the relationship between the microbiome and autism suggested that children consuming excessive antibiotics may be exposed to neurotoxic microbial metabolites [25]. According to two recent investigations, children with ASD and GI dysfunction are prone to elevated inflammatory immune responses and dysbiosis [26,27].

In one of these studies, children with autism and GI dysfunction had an imbalance of inflammatory cytokines compared to regulatory cytokines, such as transforming growth factor-beta 1 [26]. Behavioral problems have been reported to improve after modifying the microbiota, supporting the proposal that dysbiotic microbiota, their effect on the immune system, and their metabolic byproducts contribute directly to these disorders [25]. Dysfunction of the immune system is a well-recognized factor in ASD, possibly driving or creating dysbiotic microbiota [25].

Schizophrenia: Shen Y., *et al*. (2018) investigated the microbiome of patients with schizophrenia and healthy control subjects. In patients with schizophrenia, *Proteobacteria* and *Lactobacilli* were elevated, and *Firmicutes* were reduced. Altered levels of *Lactobacilli* also increased the risk of schizophrenia and were correlated with the severity of symptoms [28]. Schizophrenia is associated with changes in *Gammaproteobacteria* at the class level, *Enterobacteriales* at the order level, and *B. fragilis* at the species level [29].

A test panel for *Aerococcaceae, Bifidobacteriaceae, Brucellaceae, Pasteurellaceae*, and *Rikenellaceae* was reported to be sufficient to distinguish patients from control subjects [30]. Moreover, facultative anaerobes, such as *L. fermentum*, *Alkaliphilus oremlandii*, *Cronobacter sakazakii/turicensis*, and *Enterococcus faecium* were found in the guts of patients with schizophrenia who were medication-free [31]. A higher frequency of schizophrenia was noted in patients with *C. difficile* infection, which could be attributed to the ability of these microbes to produce phenylalanine derivatives, particularly dopamine [32,33].

The gut microbial population also responds to risperidone, an antipsychotic agent [34]. Existing cross-sectional studies have not shown causal relationships between dysbiosis and schizophrenia. Therefore, large-scale prospective studies are needed to identify the microbiome profiles associated with a higher risk of schizophrenia.

Major depressive disorder: According to Jiang H., *et al*. (2015), bacteria produce several neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid, which affect the emotional state of the host through homeostasis. The 16S rRNA sequencing analysis of fecal microbiota compositions demonstrated a significant difference between the gut microbial populations among patients with active major depressive disorder (MDD), responding MDD, and healthy control subjects [35].

While few studies identified an increased proportion of *Bacteroides, Proteus*, and *Actinomycetes* in the gut of patients with depression [36], others showed increased *Actinobacteria* and *Firmicutes* and decreased *Bacteroidetes* and *Proteobacteria* [37]. During depression, a higher relative abundance of *Bacteroidetes, Enterobacteriaceae*, and *Alistipes* and a lower relative abundance of *Actinobacteria*, *Lachnospiraceae*, and *Faecalibacterium* were found [35,38,39]. Although the gut microbiome is associated with MDD pathology, its direction remains unclear.

Posttraumatic stress disorder (PTSD): Evidence reveals that people with posttraumatic stress disorder (PTSD) demonstrate an altered gut microbiome compared to people exposed to trauma who do not develop PTSD. Freestone., *et al*. (2008) discovered that stress might alter the gut microbiome, especially *E. coli* and *Pseudomonas* [40]. According to the study results of Bajaj., *et al*. (2019), patients with PTSD had elevated pathobionts (*Enterococcus* and *Escherichia/Shigella*) and decreased *Autochthonous* genera belonging to *Lachnospiraceae* and *Ruminococcaceae* [41].

Attention-deficit hyperactivity disorder (ADHD): The gut microbiota composition is associated with ADHD risk and various manifestations of ADHD. Preliminary evidence suggests that dietary components modulating gut microbiota may influence the development of symptoms of ADHD. Patients with ADHD had more abundant Actinobacteria and less abundant Firmicutes than healthy control subjects [42].

Bifidobacterium, a member of the phylum *Actinobacteria*, plays a prominent role in the pathogenesis of ADHD, possibly by protecting intestinal barrier function, improving the immune response, and regulating dopamine synthesis through an increase in phenylalanine [43]. The levels of *Bifidobacterium* were decreased in preterm, breastfed, or C-section offspring and those administered antibiotics in the first 6 months of life [44–47].

All these factors increase the risk of developing ADHD. Pärtty., *et al*. (2015) observed decreased levels of *Bifidobacterium* in 3- and 6-month-old patients with ADHD [48], whereas Aarts., *et al*. (2017) detected slightly increased levels of the genus using a more sensitive method in a larger population [49]. It is unclear if *Bifidobacterium* can be used as a potential biomarker for diagnosing ADHD because of varying bacterial levels in these patients.

Bipolar disorders: Growing research indicates that the gut microbiota of patients with bipolar disorder is different from that of normal individuals. In patients with bipolar disorder, *Clostridiaceae*, phylum *Actinobacteria* and class *Coriobacterium* are more abundant [50], and *Faecalibacterium* is reduced [51,52].

In patients with bipolar disorder, *Lactobacillus* counts were negatively correlated with sleep, and *Bifidobacterium* counts were negatively correlated with serum cortisol levels, as reported by Aizawa (2018) [53]. The bacterial changes noted in patients with bipolar disorders in different studies are not entirely coincidental.

Anxiety disorders: Anxiety disorders are associated with inflammatory processes, possibly influenced by gut bacteria. Patients with a generalized anxiety disorder had elevated *Bacteroides*, the core genus of the phylum *Bacteroidetes*, and decreased *Faecalibacterium*, *Eubacterium rectale*, *Lachnospira, Butyricicoccus*, and *Sutterella*.

In patients with generalized anxiety disorder, *Ruminococcus gnavus* and *Fusobacterium* proportions were significantly increased, leading to invasive and pro-inflammatory conditions and increasing intestinal permeability [54]. The abundances of *Eubacterium, Ruminococcaceae,* and *Prevotella* in the intestine were negatively correlated with the severity of anxiety and positively with the reduction of anxiety.

In contrast, the abundances of *Bacteroides* and *Escherichia-Shigella* were positively associated with the severity of anxiety [55]. However, the role of dysbiosis in other forms of anxiety disorders—such as agoraphobia, panic disorder, social anxiety disorder, specific phobias, and separation anxiety—remains unclear.

The microbiota has been shown to have an anxiety-inducing or anxiety-relieving effect in humans. Jiang., *et al*. (2018) opined that anxiety disorders might develop due to an imbalance of the GI flora, either impoverished or disrupted by antibiotics [56].

Sleep disorders: In the 1960s, researchers began studying the association between gut microbiome and sleep. Muramyl peptides, a mysterious compound found in many bacterial species, were related to sleep. Later, microbes and circadian genes were found to be inextricably linked. In about 20% of the commensal species, 60–80% of the total bacterial composition oscillates at a rhythmic rate (e.g., *Clostridiales*, *Lactobacillales*, and *Bacteroidales*) [57].

In addition to modulating the host's activities structurally and functionally, this oscillation affects rhythmic food intake, diet, and biological time [57–59]. Circadian clock misalignment, sleep deprivation, and shift experience affect gut microbial communities [60]. Jet lag, for example, is marked by a decline in *Christensenellaceae, Dorea, Anaeroplasmatales, Anaeroplasmataceae, Anaeroplasma*, *Lactobacillus*, *Lactococcus, RF32, Alphaproteobacteria, Proteobacteria, Ruminococcus*, and *L. ruminis,* and an increase in *Paraprevotella* and *Fusobacteria* [57].

Similarly, mice exposed to sleep fragmentation for 4 weeks exhibited gut flora dominated by *Lachnospiraceae* and *Ruminococcaceae*, with a gradually reduced relative abundance of *Lactobacillaceae* [61]. In young people with partial sleep deprivation, an increase in the ratio of *Firmicutes* to *Bacteroidetes* was observed in the gut [62]. Circadian rhythms are caused by the microbiota and influence epigenetic changes and metabolite oscillations in the host [58].

Intestinal microbiological rhythms are closely associated with alterations in specific host circadian genes, such as *Bmal1*, *Per1*, and *Per2* [63]. Similarly, in narcolepsy, *Bacteroidetes* and *Flavonifractor* were predominant in the global bacterial community structure [64]. Insomnia is also strongly associated with gut microbiota dysbiosis. A redundancy analysis by Liu., *et al*. (2019) demonstrated a high correlation between the gut microbiota and clinical sleep parameters [65].

Eating disorders: Concerning eating disorders, the role of intestinal microbiota has been investigated only in anorexia nervosa (AN). A randomized, double-blind placebo-controlled trial reported decreased microbial diversity and secondary bile acid concentrations in the vancomycin-treated vancomycin-treated group at 7 days [66]. Initially, the microbial profiles of a small number of patients with AN were compared to those of obese and control individuals [67].

Significantly higher levels of *Methanobrevibacter smithii*, a commensal enteric microbe belonging to the Archaea domain, were found in patients with anorexia nervosa (AN), suggesting the involvement of the microbe in promoting constipation, a symptom frequently observed in these individuals [68].

Also, patients with AN had lower levels of specific taxa belonging to genera *Streptococcus*, *Clostridium,* and *Bacteroides* and decreased concentrations of the fecal SCFAs acetate and propionate [69,70]. This shift in the microbial population also resulted in elevated fecal branched-chain fatty acids (protein fermentation products) [70].

Substance abuse disorder (SUD): Drug abuse is associated with increased bacterial dysbiosis. Compared to healthy control subjects, the species diversity index and number of *Paracoccus, Thauera* and *Prevotella* were considerably higher in patients with substance abuse disorders (SUDs) [71].

Bacteria from genera *Bacteroides* and *Haemophilus* were consistently less abundant than those from genera *Prevotella*, *Phascolarctobacterium*, and *Ruminococcus* in individuals with SUDs in healthy control subjects and those with long-term SUDs than those with short-term SUDs [71].

Regarding investigations on SUDs, most human studies have focused on alcohol abusers. Approximately 31% of alcoholic abusers have dysbiosis [72]. Stool samples of alcoholics demonstrated decreased *Firmicutes* (specifically, *Lactobacilli,* and *Enterococci*) and *Actinobacteria* (specifically *Bifidobacteria*) [73].

Variability in types of alcoholic beverages consumed, the amount consumed, frequency of alcohol intake, and presence or absence of concomitant alcoholic liver disease may contribute to differences in the microbiome profiles in alcoholics [74]. Interestingly, binge drinking in healthy adults with no prior history of alcohol abuse disorder is also associated with a modest increase in serum liposaccharide (LPS) and 16S rDNA and elevated levels of inflammatory cytokines, indicating that acute alcohol exposure may also alter gut permeability and facilitate bacterial translocation into the circulatory system [75].

Studies in patients with opiate-induced constipation and cocaine-induced bowel ischemia indicate that opiate use causes gut dysbiosis, and treatments that relieve constipation (e.g. probiotics) restore changes in the gut microbiome. Mora., *et al*. (2012) reported that the use of opioid analgesics disrupts gut homeostasis, leading to increased susceptibility to infections from *C. difficile* [76].

No changes specific to heroin, methamphetamine, or ephedrine were observed in the gut microbiota. Nicotine, another commonly used substance of abuse—consumed either as smoking cigarettes or chewing tobacco—affects gut health, altering the microbiome and adversely impacting overall health. In smokers, the relative abundance of *Prevotella* was higher, while *Bacteroides* was lower. The Shannon diversity index (a measure of diversity) was also lower in these individuals [77].

In current smokers, *Erysipelotrichi-Catenibacterium taxa* and *Alphaproteobacteria* were more prevalent, and the abundance of *Bacteroidetes* and *Proteobacteria* at phylum level was decreased [78]. On the contrary, smoking cessation increased the abundance of *Firmicutes* and *Actinobacteria* in smokers. The effects of drug abuse on the intestinal microbiome content in humans are presented in Table 1.

Drug	Effect on Gut Microbiome
Alcohol	↓ *Bifidobacteria*, ↓ *Enterococci*, ↓ *Lactobacilli*
Alcohol	↑ *Bacteroidetes*, ↓ *Firmicutes*
Alcohol	↑ *Proteobacteria*, ↓ *Bacteroidetes*
Alcohol	↑ *Lachnospiraceae*, ↓ Overall bacterial load, ↓ *Ruminococcaceae*
Cocaine	↑ *Bacteroidetes*, ↓ *Firmicutes*
Heroin, methamphetamine, ephedrine	No changes specific to heroin, methamphetamine, or ephedrine
Opioids	↑ Alpha diversity
Opioids	↓ *Bacteroidaceae*, ↓ *Clostridiales* XI, ↓ *Ruminococcaceae*
Opioids	↑ *Bifidobacterium*
Nicotine	↑ *Prevotella*, *Erysipelotrichi-Catenibacterium* lineage, *Alphaproteobacteria*, ↓ *Bacteroidetes* and *Proteobacteria*

Table 1: *Effects of drugs of abuse on gut microbiome contents in humans [78,79].*

Neurological (cognitive) diseases

The GI tract and its resident microbiota can undergo progressive functional decline with aging and neurological conditions such as stroke, Alzheimer's disease (AD), and Parkinson's disease (PD).

Alzheimer's disease: The gut microbiota can influence AD development in several ways. AD may be caused, in part, by bacteria or bacterial endotoxins [80]. Amyloids and LPS, bacterial products associated with AD, accumulate in the blood and brain [81]. Certain bacterial species of *Firmicutes, Bacteroidetes,* and *Proteobacteria* produce amyloids that induce pro-inflammatory cytokines IL-17A and IL-22, resulting in AD [80]. Changes in the gut microbiota can also trigger pro-inflammatory cytokines in the body, causing intestinal permeability. Aβ toxicity in the brain and blood-brain barrier (BBB) permeability increases due to intestinal permeability [82].

Patients with cognitive impairment and brain Aβ deposition had a lower fecal abundance of anti-inflammatory *E. rectale* and *B. fragilis,* and a higher abundance of pro-inflammatory *Escherichia* spp. and *Shigella* spp. compared to patients with cognitive impairment with no Aβ deposition or healthy control subjects [83].

Parkinson's disease: Although the etiology of PD remains unclear, the gastrointestinal tract is involved as it is the source of several toxins, such as Lewy bodies, that affect the central nervous system (CNS), as in PD [84–86]. In patients with PD, there was decreased representation of *Prevotellaceae, Coprococcus*, *Firmicutes*, *Clostridium coccoides*, *C. leptum*, and *Bacillus fragilis* and increased representation of *Lactobacillaceae, Verrucomicrobiaceae, Ruminococcaceae, Lactobacillus, Bacteroidetes, Proteobacteria*, *Clostridiaceae*, and *Akkermansia* [87–89].

Small intestinal bacterial overgrowth was associated with motor fluctuations, and eradicating bacterial overgrowth improved clinical symptoms in these patients [90]. Specific genes associated with LPS production and "pro-inflammatory" bacterial taxa such as *Akkermansia* and *Ralstonia* are reported to be elevated in this patient population [86].

Dysbiosis and HIV infection

Gut-resident bacteria also regulate the mucosal immune system. Acquired immunodeficiency syndrome (AIDS) results from chronic systemic inflammation and dysregulation of the intestinal immune barrier caused by human immunodeficiency virus (HIV) infection. In patients with HIV infection, a mucosal-adherent dysbiotic bacterial community enriched in *Proteobacteria* and depleted of *Bacteroidia* members was associated with markers of mucosal immune disruption, T-cell activation, and chronic inflammation [91].

Enterobacteriaceae, such as *Klebsiella*, *Citrobacter*, and *Salmonella*, actively promote an inflammatory environment in the GI tract that supports their proliferation and persistence [91]. In addition, Garrett., *et al*. (2017) confirmed that disruption of the mucosal immune system could develop a dysbiotic pro-inflammatory community sufficiently potent to sustain pathologic, chronic inflammation [92].

Additionally, this dysbiosis was also evident in HIV-infected patients receiving anti-AIDS therapy, with an inverse association between the activity of the kynurenine pathway and plasma IL-6 concentration [91].

Mechanism of dysbiosis-induced psychological disorders

There are three pathways by which the gut microbiota affects brain function on the microbiome-gut-brain axis [93]:

1. In the immunoregulatory pathway, the microbiota affects the production of cytokines, cytokinetic reaction factor, and prostaglandin E2 in the immune cells, resulting in brain abnormality [94].

2. The neuroendocrine pathway operates via > 20 types of enteroendocrine cells in the intestine [95]. Through regulating neurotransmitters, such as cortisol, tryptophan, and serotonin (5-HT), the gut microbiome may influence the hypothalamic-pituitary-adrenal (HPA) axis and CNS [95].

3. This pathway acts through the enteric nervous system. The sensory neurons of the myenteric intestinal plexus are exposed to the gut microbiota. Altered functioning of sensory and motor neurons in the intestine dysregulates motility and gut hormone secretion [96]. Furthermore, the intestinal nervous system forms synaptic connections with the vagus nerve, linking the brain to the intestine [96]. This network can be described as the gut microbiota-enteric nervous system-vagus-brain information transmission pathway. Also, neurotoxic metabolites, such as D-lactic acid and ammonia, from the gut microbiota can pass via the vagus nerve into the brain, affecting brain function, stress responses, and sleep [97].

Through these three pathways (Figure 2), the CNS can regulate the intestinal microbiota composition. By controlling intestinal peristalsis and epithelial cell function, the HPA axis affects the environment of the intestinal microbes [98]. Also, the circulatory system regulates the effects of various metabolites, induced or produced by the microbiota, on the CNS. Among them are neurotransmitters, hormones, precursors of neurotransmitters and hormones, and SCFAs. Metabolites can pass through the intestinal barrier, enter the circulation, and cross the blood-brain barrier (BBB), affecting neurological function.

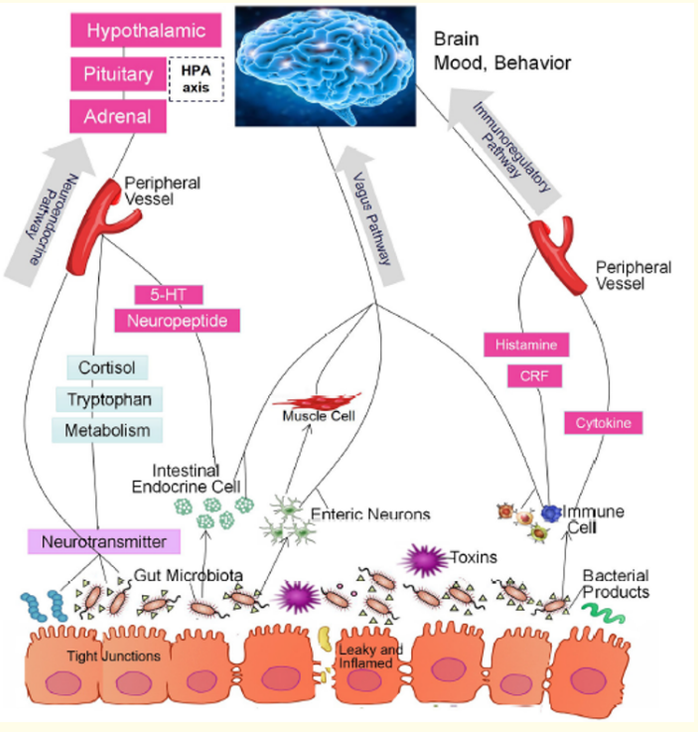

Figure 2: *Microbiota in the gut modulates brain function by associating the immune system, neuroendocrine system, and vagus nerve. Adapted from Li., et al. (2018) [99].*

Right: Immunoregulatory pathway activated by interaction of bacterial products with immune cells followed by altering the levels of cytokines, cytokinetic reaction factor, and prostaglandin E2 affect the brain functions.

Middle: Vagus nerve pathway activated by the exposure of the sensory neurons of the myenteric intestinal plexus to the gut microbiota. This reaction alters intestinal motility and gut hormone secretion.

An information transmission pathway could be described as gut microbiota-enteric nervous system-vagus-brain, which links the intestine to the brain through synaptic connections in the intestinal nervous system and vagus nerve. Similarly, neurotoxic metabolites produced by the gut microbiota, such as D-lactic acid and ammonia, can enter the central nervous system, affecting brain function, stress responses, and sleep.

Left: Neuroendocrine pathway is activated by more than 20 types of enteroendocrine cells in the intestine. The gut microbiome regulates the secretion of neurotransmitters such as cortisol, tryptophan, and serotonin (5-HT) from these cells and alters the functions of the HPA and CNS.

Management of dysbiosis-induced psychological disorder

Microbiota dysbiosis may play a role in developing certain neurological diseases. Mounting evidence suggests that interventions restoring the microbiota homeostasis and intestinal barrier integrity can benefit particular disorders' and diseases' clinical courses and symptoms [84]. Bravo., *et al*. (2012) concurred that probiotics, defined as living organisms providing health benefits to the host, are the most commonly preferred therapy for gut dysbiosis [100].

Probiotics suppress pro-inflammatory cytokine levels and enhance intestinal barrier integrity. They also protect neurons by preventing stress-induced synaptic dysfunction [101]. Prebiotics, such as fructooligosaccharides and galactooligosaccharides, are soluble fibers that stimulate the preexisting gut microbiota. Prebiotics confer anxiolytic and antidepressant effects—similar to those of probiotics—by reducing stress-induced changes in the colonic microbiota, and creating stabilized levels of the *Bifidobacteria* and *Lactobacilli* populations [102]. Antibiotics are also widely used in clinical settings for dysbiosis.

Ciprofloxacin, rifaximin, and cotrimoxazole are well-known antibiotics used to treat intestinal infections resulting from dysbiosis. Elusive alterations in the gut microbiota by dietary inventions and physical activity could be a practical approach to manipulate microbes, and improve the symptoms of psychological disorders. Abnormality in SCFAs, following dysbiosis, is a common cause of brain diseases. Thus, increasing SCFAs—through fiber-rich nutrition in combination with the appropriate gut microbial composition—can be a beneficial treatment approach.

Conclusion

The gut-brain axis links the central and enteric nervous systems. The gut microbiota influences the interactions between the intestines (gut microbiota) and the psychological (emotional) brain centers. It signals the brain, and the brain sends signals to the gut microbiot via neural, endocrine, immune, and humoral links.

Current research suggests that gut dysbiosis may underlie specific psychological conditions, disorders, diseases, and behaviors. Thus, future research should investigate these potential and profound connections to cure or prevent or ameliorate such conditions, disorders, and diseases.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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Volume 11 Issue 3 March 2022