


REVIEW

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Bridging the gap: associations between gut microbiota and psychiatric disorders



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Abstract

Background Gut microbiota plays a pivotal role in the gut-brain axis and can influence neurodevelopment and mental health outcomes. This review summarizes the current evidence on the associations between gut microbiota alterations and various psychiatric illnesses.

Main body The composition of the gut microbiome evolves from birth through old age, and disruptions during critical periods may increase disease risk. Factors like diet, medications, stress, and infections can disturb the gut microenvironment and lead to dysbiosis. Dysbiosis has been linked to conditions like depression, anxiety, autism, ADHD, and schizophrenia. Proposed mechanisms involve microbial regulation of neurotransmitters, inflammation, oxidative stress, blood-brain barrier permeability, and the immune system. Therapeutic strategies like probiotics, prebiotics, and faecal transplantation may modulate the gut-brain axis and microbial ecosystem. However, more research is needed to elucidate the causal microbiota-psychiatry relationship. Understanding gut-brain interactions may uncover new possibilities for preventing and managing psychiatric disorders.

Conclusion A growing body of research points to a close relationship between gut microbiota and mental health. While the field is still emerging, dysbiosis of gut microbial ecosystem has been associated with various neuropsychiatric conditions. The underlying mechanisms likely involve the microbiota-gut-brain axis signalling pathways. Additional research with larger samples is required to establish causal links between specific microbial changes and psychiatric outcomes.

Keywords Microbiota, Psychiatric disorders, Dysbiosis, Probiotics, Psychobiotics

Background

The gastrointestinal tract and brain are linked through a sophisticated, bidirectional communication network known as the gut-brain axis [1]. As a result of studies demonstrating revealing the substantial impact of gut microbiota on signalling connections between the gut

and brain and its involvement in the gut-brain axis, the term was revised to the microbiota-gut-brain axis. This axis governs the functions of the central nervous system (CNS), gut, and immunity [2]. In healthy individuals, gut microbiotas establish stable host-bacterial mutualism. Any disruption to this mutualism would adversely affect the functioning of the brain, digestive system, and metabolism [2]. Bidirectional signalling between the gut microbiota and the CNS can affect the reaction to stress, feelings of pain, neurochemical amounts, and gut-brain axis disorders [1, 3]. The interaction between the gut microbiome and the nervous system involves metabolic processes such as tryptophan, serotonin, immunity, gut hormonal, and short-chain fatty acid metabolism (SCFAs) [4]. SCFAs play a crucial role in regulating the release of important neurotransmitters, including

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enteroendocrine serotonin (5-HT) and peptide YY (PYY), a neuropeptide critical to the gut-brain axis [5]. Research has demonstrated that the intestinal microbiota can influence the behaviour of germ-free (GF) animals and alter the physiology and biochemical properties of the nervous system [6].

The hypothalamic-pituitary-adrenal axis (HPA) is a pivotal component of the neuroendocrine system, regulating various physiological processes, including digestion, immunity, behaviour, and stress responsiveness. Abnormal development of the HPA is observed in GF rodents, leading to a modified stress response and decreased expression of brain-derived neurotrophic factor (BDNF) [7]. If GF mice are colonized with normal gastrointestinal microbiota from conventionally reared mice or the probiotic *Bifidobacterium infantis*, these abnormalities might be reversible [7]. These findings underscore the regulatory role of gut microbiota in HPA activity and emphasize its critical contribution to the development of the nervous system.

Gut microbiota and brain development

While the human body is nearly sterile at birth, the gut is quickly colonized by bacteria. This colonization process continues throughout childhood and adolescence. Consequently, establishing and progressing intestinal microbiota during infancy may shape an individual's future physical and mental well-being. Brain development throughout childhood and adolescence is of equal importance, mirroring the progression and maturation of intestinal microbiota. Potential disruptions in the mutualism between the host and microbiota during these periods may have long-lasting health effects, increase the risk of neurodevelopmental disorders, and modify gut-brain axis pathways. Moreover, the fragility and immaturity of intestinal microbiota during these stages render individuals more susceptible to environmental influences, including antibiotics, stress, inadequate nutrition, infections, and more. This susceptibility leads to gut microbiota dysbiosis, which is detrimental to physical and mental health and ultimately contributes to brain disorders [8]. Despite the fact that gut microbiota is typically more established and stable in maturity, synaptic pruning and myelination still take place [9]. Changes in intestinal microbiota that occur during this period may therefore influence brain function and behaviour. It is critical to preserve a robust intestinal microbiota during all stages of development, maturation, and colonization to avert age-related brain diseases.

Even though the ageing process does not represent a pivotal phase in neurodevelopment, inflammation is a prevalent occurrence within the body [10]. It manifests as a progressive chronic proinflammatory response. The

progressive alteration of gut microbiota composition [11] caused by this response degrades the stability and diversity of microbiota [12]. The gut microbiota composition in older adults is frequently influenced by factors such as the living environment, dietary patterns, and individual health status [12]. Furthermore, factors such as drug use, impaired immunity, malabsorption of nutrients, and deterioration of digestive motility have an effect on the composition of the gut microbiota [13].

Role of microbiota in brain function

Microbiota produce different neuroactive molecules or neurotransmitters that maintain the communication between gut and brain such as acetylcholine, GABA, and serotonin [14, 15]. Interestingly, 90% of serotonin required for mood, behaviour, sleep, and other CNS functions is produced in the gut [16]. Serotonin binding to 5-HT receptors on the microglia induces another mechanism for gut-induced modulation of neuroinflammation [17]. Similarly, tryptophan, which is a serotonin precursor, can influence microglia activity and the transcriptional programme of astrocytes [18].

In addition, bacterial fermentation of indigestible dietary fibres produces SCFAs such as butyrate, propionate, and acetate [19]. A small fraction of SCFAs reaches the systemic circulation and cross the blood-brain barrier (BBB) restoring its integrity [20]. Moreover, SCFAs can restore the normal maturation process of the microglia [21] and modulate neurotransmitters, like glutamate, glutamine, GABA, and neurotrophic factors [22]. Propionate and butyrate can influence the cell signalling system and regulate the expression levels of tryptophan 5-hydroxylase 1, involved in the synthesis of serotonin, and tyrosine hydroxylase, which is involved in the biosynthesis of dopamine, adrenaline, and noradrenaline [23].

Impact of the mode of delivery on microbiota composition

The “sterile womb dogma” held for an extended period that the human foetus remains sterile until delivery, and that microorganisms begin to colonize gastrointestinal tract after delivery. However, previous research reported that microbial colonization begins in utero [24–26]. Colonization by *Staphylococcus epidermidis*, *Enterococcus faecium*, and *Escherichia coli* might occur through translocation via the bloodstream and placenta from the mother's gut [8]. Vaginal versus caesarean section (CS) delivery mode significantly impacts newborn GI tract colonization [27, 28]. Despite lack of medical indication, CS rates continue rising, exceeding 50% in some countries [29].

Vaginally delivered (VD) infants' gut microbiota resembles the maternal vaginal microbiota, dominated

by *Lactobacillus*. Meanwhile, CS leads to an imbalance and decreased diversity, lacking exposure to the vaginal microbiota of mother. Pathogens from the hospital dominate initial contact [30]. Infants delivered vaginally have higher *Sneathia*, *Bacteroides*, *Corynebacterium*, *Staphylococcus*, *Clostridium difficile*, lower *Lactobacillus*, *Prevotella*, and Bifidobacteria, compared to those born by CS [27]. Colonization of microbiota plays a vital role in infant metabolism, immunity, and brain development [31]. Maternal stress may also impact infant nervous system development by altering vaginal microbiota and subsequent intestinal colonization [32].

Factors affecting the changes of gut microbiota in psychiatric diseases (see Fig. 1)

Diet

Diet powerfully impacts the diversity and immunology of microbiota [33]. The Mediterranean diet with fish oil reduced symptoms of depression in one study [34]. However, another study found that vegetarian/vegan diets were associated with increased depression risk [35]. The high-fat, low-carbohydrate ketogenic diet improved cognition and memory in Alzheimer’s disease [36]. Despite the hypotheses that obesity is associated with increased Firmicutes/Bacteroidetes ratio, weight loss diets did not significantly alter this ratio [37]. However, the effect of diet-driven microbiota changes on the colon health and metabolism requires further studies [38].

Probiotics

Probiotics could be used in treatment of mental disorders which involve increased intestinal permeability like depression, anxiety, autism, and schizophrenia [39, 40]. Specific strains differentially impact the brain. A meta-analysis found that probiotics significantly alleviate symptoms of depression [41]. In healthy volunteers, *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 given for 30 days reduced Hospital Anxiety and Depression Scale scores versus placebo [42]. Also, other strains like *Lactococcus lactis*, *B. longum*, *Lactobacillus bulgaricus*, *Bifidobacterium animalis*, *Streptococcus thermophilus*, and *L. helveticus* decrease depression and stress [43]. Probiotics decreased inflammation and improved behavioural symptoms in patients with autism spectrum disorder (ASD) [44]. In schizophrenia, probiotics with vitamin D given for 12 weeks improved Positive and Negative Syndrome Scale (PANSS) scores, suggesting utility countering gastrointestinal inflammation [45]. Probiotics may also improve COVID-19-associated mood disturbances by restoring intestinal balance and preventing pathogen overgrowth [46, 47]. However, limitations exist, like avoiding probiotics in immunocompromised patients on corticosteroids [46].

Stress

The HPA axis dysregulation from early-life stressors increases risk for affective and anxiety disorders [48]. Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) drive the HPA axis, influencing neurotransmission, sleep, mood, and feeding [49].

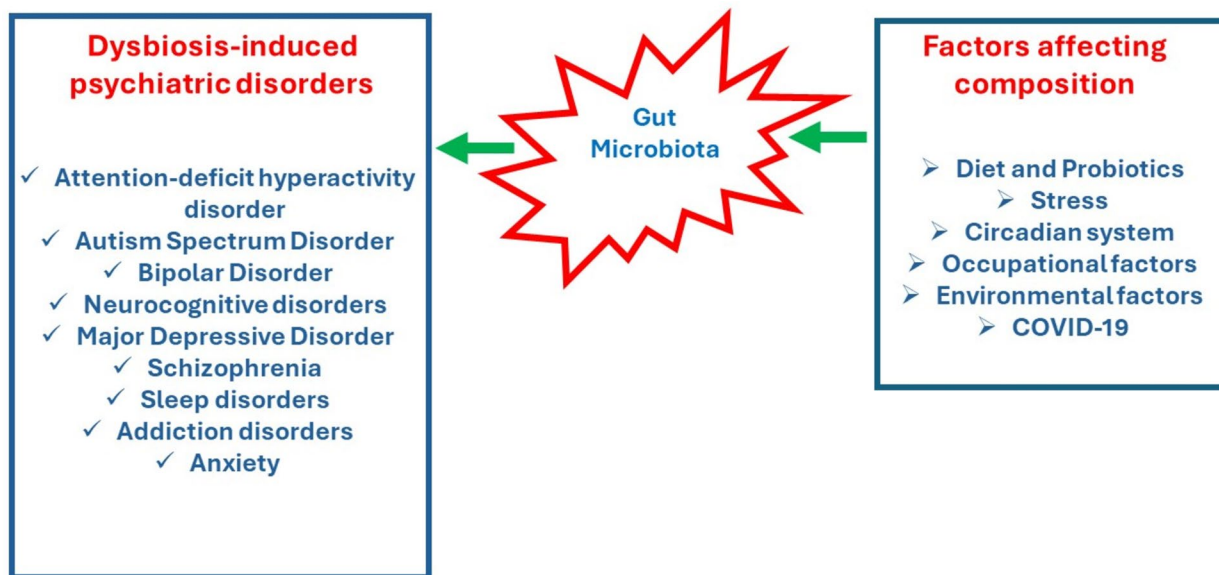


Fig. 1 Factors affecting gut microbiota composition and the psychiatric diseases affected by dysbiosis

Communication between the nervous and endocrine systems regulates body functions [50]. Depressive disorders also show serotonin deficiency and HPA axis hyperactivity [51]. Stress reduces *Lactobacillus* and *Bifidobacterium* and increases *Clostridium* and *Escherichia coli* through catecholamine and glucocorticoid secretion [52].

Circadian system

The circadian system includes the suprachiasmatic nucleus central clock and peripheral clocks like the intestine. The gut microbiota shows diurnal fluctuations affected by shift work, light, sleep, diet, and stress [53]. Disrupting the circadian clock may contribute to psychiatric and metabolic disorders by altering gut microbiota signalling [54]. Bacterial clocks may also regulate human circadian rhythms and behaviour [55].

Occupational and environmental factors

Workplace biological (animal contact), chemical (metalworking fluids, pesticides), and physical (pressure, travel) exposures alter the microbiome [56]. After 30 days at sea, sailors showed increased *Streptococcus gordonii* and *Klebsiella pneumoniae* [57]. Night shift workers had increased Firmicutes, Actinobacteria, *Dorea*, and *Faecali* bacterium versus day workers [54]. These microbiome changes could serve as occupational health biomarkers [53]. Environmental pollutants like heavy metals, pesticides, polycyclic aromatic hydrocarbons (PAH), and polychlorinated biphenyls (PCB) also modify the microbiota [58]. Early chlorpyrifos exposure caused chronic microglial dysregulation, increasing Alzheimer's disease risk [59]. However, microbes can detoxify xenobiotics, sometimes generating more toxic byproducts [60].

The coronavirus-19 (COVID-19)

Depression in COVID-19-infected patients could be due to social factors such as the social quarantine or pathological factors such as changes in the HPA axis, CNS proinflammatory cytokines, microglial production of inflammatory cytokines, or injury to the hippocampus [61].

Recently, post-acute COVID-19 syndrome (PACS) or long COVID-19 was a recent term used to describe a syndrome which is characterized by the persistence of clinical manifestations that persist 4 weeks after the onset of acute symptoms of COVID-19. Psychological issues that could persist after COVID-19 include anxiety, depression, insomnia, cognitive impairment, and posttraumatic stress disorder (PTSD) [62–68].

Gut microbiota diversity and beneficial bacteria predominance affect COVID-19 infection. After clearance of COVID-19, the gut microbiome remains dysbiotic, with fewer beneficial bacteria. Patients with PACS had higher

levels of *Ruminococcus gnavus* and *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii*. Moreover, patients with PACS who suffer neuropsychiatric symptoms had higher level of *Clostridium innocuum*, and *Actinomyces naeslundii* [69].

Antibiotics, antivirals, antifungals, and steroids, as well as diabetes, hypertension, and old age, worsen this dysbiosis [70]. Therefore, microbiota modification using probiotic could play a potential beneficial role as an adjunctive therapy in COVID-19 infection and is still an ongoing research process [71].

Role of gut microbiota in psychiatric illnesses

Attention-deficit hyperactivity disorder (ADHD)

ADHD is a common neurodevelopmental disorder affecting millions of children [72]. Genes for dopamine receptors and transmitters are the main etiological factors [73]. Growing evidence indicates a gut-brain connection [73]. ADHD patients showed increased *Actinobacteria* (e.g. *Bifidobacterium*) and reduced Firmicutes versus controls, with enhanced dopamine precursor synthesis capacity [74]. However, a meta-analysis found no significant microbiome differences beyond increased *Blautia* in ADHD, which regulates the metabolism and inflammation [75]. More research is needed in demographically diverse cohorts [76] and in assessing ADHD with other comorbidity [77–79]. Early probiotic administration like *Lactobacillus rhamnosus* GG may reduce ADHD risk by modulating emotional behaviour and GABA receptor expression [80]. Dietary improvements like reducing food additives and increasing omega-3 polyunsaturated fatty acids (PUFAs) can also minimize ADHD hyperactivity [81].

Autism spectrum disorder (ASD)

ASD is a neurodevelopmental disorder that is hazardous and is characterized by gastrointestinal symptoms [82]. While genetic factors, gastrointestinal abnormalities, inflammation, and environmental exposures are plausible contributors, no single factor can account for ASD [83]. Patients diagnosed with ASD exhibited dysbiosis characterized by a phylum number of *Fusobacteria*, *Verrucomicrobia*, Firmicutes, and *Bacteroides*, as well as a ratio of Firmicutes to *Bacteroides*. The authors also reported that the alterations impact the concentrations of volatile organic compounds (VOC) and short-chain fatty acids (SCFAs) in individuals diagnosed with ASD. These volatile organic compounds include indole, a precursor to serotonin and melatonin and a metabolite of tryptophan [83]. Nevertheless, these findings must be interpreted with caution due to the potential impact of antibiotic therapy or individualized dietary regimens on individuals diagnosed with ASD [1].

Bipolar disorder (BD)

BD is a persistent mood disorder characterized by alternating manic and depressive episodes [84]. It was clinically observed that longer untreated illness in bipolar I disorder lead to more symptoms severity [85]. On the other hand, TRYCATs are neuroregulatory tryptophan catabolites, oxidative and nitrosative stress, and immune-inflammatory indicators found in patients [86]. Dysbiosis of the gut microbiota could be linked to the development of BD [87]. Increased Coriobacteriaceae associates with higher cholesterol, while more *Lactobacilli* associates with obesity in BD [88, 89]. Reduced *Faecalibacterium*, an anti-inflammatory commensal, also correlates with BD [90]. Clostridiaceae, which produce mood-regulating SCFAs, were four times lower in BD [91]. Previous research observed *Toxoplasma gondii* among patients with schizophrenia and bipolar disorder [92] that might affect gut microbiota in these patients and trigger conditions.

Neurocognitive disorders

Cognitive function preclinical studies, such as GF/GI infection models, antibiotic treatment, dietary manipulation, and probiotic treatment, have shown that gut microbiota composition affects cognitive function [93–96]. Prebiotics can improve emotional attention performance in healthy individuals [97], and probiotics can modify brain activity during a comparable test [98]. Furthermore, previous research found a significant relationship between Alzheimer disease and gut microbiota dysbiosis. A higher abundance of *Prevotella* species and lactic acid bacteria was correlated with cognition [99]. Targeting gut microbiota for cognitive benefits may be effective at age extremes, when brain function is vulnerable and in flux, with rapid development in infancy and gradual decline in function with a steady decline in specific cognitive abilities in old age [100]. A small randomized controlled trial revealed that microbiota-targeted therapies may benefit age-related cognitive impairment [101]. Also, previous research found cognitive impairment in schizophrenia and bipolar [102] that might elicit indirect relation of gut microbiota in cognitive impairment. No research has been conducted on the effectiveness of microbiota supplementation in boosting cognitive development in infants. However, preclinical research indicates that gut microbiota significantly impacts neurodevelopment throughout important postnatal periods [7, 103, 104] that might relate to hormonal disturbance. Similarly, previous research found prevalence of psychosis and depression in postnatal period was increased and

mostly related to hormonal impairment especially postpartum [105, 106].

Major depressive disorder (MDD)

Many of the factors described in the data which established a connection between this mental disorder and intestinal microbiota components were validated by Naseribafrouei et al. [107].

There was a notable increase in the prevalence of MDD among patients [106, 108], who were correlated with elevated levels of the valeric acid-containing *bacterium Oscillibacter* and the inflammation-associated genus *Alis-tipes*. In a mouse model, Zhang et al. [98] established a correlation between dysbiosis of the microbiota and systemic inflammation as well as raise intestinal permeability [109]. The alteration of microbiota composition of mice caused by endogenous melatonin reduction (EMR) included an increase in the relative abundance of *Lactobacillus*, a decrease in the abundance of *Bacteroidetes*, and a modification in the ratio of Firmicutes/Bacteroidetes. Furthermore, EMR rodents exhibited increased systemic inflammation and enhanced gut permeability, which was manifested as a leaky gut. Utilizing SCFA quantification to analyse the microbiota composition of individuals diagnosed with MDD may prove effective. In a study on the SCFAs profile involving 116 women, it was found that 40.52% of the participants reported experiencing depression [110]. The results of the study indicated that the proportion of propionic acid was reduced among the participants, while isocaproic acid was higher, in comparison to the composition of healthy subjects. However, the inability to definitively assert that SCFAs contribute to the depressive phenotype was attributable to the small sample size. Studies on animal models have established a correlation between the composition of intestinal microbiota and personality traits and behaviour, including anxiety and depression. After transplanting the gut microbiota of confident Mongolian gerbils (*Meriones unguiculatus*), Gan et al. [111] observed alterations in the behaviour of timid individuals. After “bold faecal microbiota” transplantation, timid gerbils frequently displayed courageous behaviour, suggesting a correlation between the gut microbiota and the disposition of the host [112].

Schizophrenia (SCZ)

Schizophrenia is a complex condition affecting emotional, vocational, and cognitive abilities [113]. Viruses, cardiovascular, and metabolic diseases increase the risk of premature mortality among SCZ patients [114]. Owen et al. identified three distinct dimensions in SCZ: negative symptoms, positive symptoms, and

cognitive impairment [115]. Moreover, schizophrenia could be induced by other medical disease [116] or drugs [117, 118].

The objective of neuroimaging and biochemical research is to elucidate the pathogenesis of SCZ. So far, neurotransmitter dependencies have been found, which may explain SCZ clinical manifestations. In this pathophysiology, dopamine appears to be the most important neurotransmitter [119]; however, other studies suggest that dopamine had an indirect function and identified other neurotransmitter linkages [120, 121]. Kozłowska et al. linked the etiology of SCZ to immune/inflammatory processes, where host alarmins activate signalling pathways, causing several infection-induced or sterile inflammatory disorders. A rising body of research highlights the importance of the glutamatergic system [122]. Specifically, the neuregulin 1 gene on 8p12 and the G72 and G30 genes on 13q33, which activate DAOA, are of concern [123]. These genes confirm the neurodevelopmental idea of SCZ and the glutamatergic system's participation [124]. Increasing mesolimbic dopaminergic transmission and inhibiting glutamatergic transmission are known to contribute to favourable SCZ symptoms. The growing number of premises suggests that kynurenic acid (KYNA) may modulate both pathways [125]. KYNA functions as an α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and an antagonist of the NMDA receptor complex's strychnine-independent glycine site. SCZ patients have higher CSF KYNA levels, according to research. KYNA study revealed its potential function in CNS physiology and disease. KYNA influences CNS function and illness symptoms, although the mechanism is unknown. However, significant KYNA concentration disparities between sick and healthy individuals suggest its role in the development of neurological and mental diseases [126]. KYNA is difficult to detect in the blood due to its low penetration of the blood-brain barrier. Therefore, scientists focus on other metabolites in the kynurenine pathway. Previous study found a predicted concentration of 3-hydroxykynureine for reducing psychopathological symptoms in the first episode of SCZ [127]. The discovery of biological variables that predict antipsychotic medication success is promising. Despite thorough investigation, there is still no known cure for psychotic disorders, including SCZ, and the etiopathogenesis of this baffling and incurable disease remains unknown [112].

Sleep disorders

Gut microbiota and sleep interact bidirectionally. Microbial colonization in early development coincides with critical cognitive phases [128]. Sleep loss alters microbiota diversity and composition in adulthood [129, 130];

also, short sleep fragmentation impacts gut bacteria and metabolism over time [130].

In obstructive sleep apnea, microbiota dysbiosis relates to inflammation in children [131]. Foecal transplants from sleep apnea mice increase sleep in naive mice, suggesting that the microbiota mediates sleep-wake changes [132]. Patients with acute and chronic insomnia show gut dysbiosis [133]. Therefore, microbes that produce sleep neurochemicals like GABA, serotonin, and histamine may hold therapeutic potential [134].

As mentioned early, the circadian disruptions in humans and mice alter microbiota diversity [54]. Light exposure, melatonin, and microbiota-targeted treatments may readjust circadian rhythms [135, 136]. Microbiota also relates to sleep disorders in psychiatric conditions [137, 138]. Overall, the microbiota-gut-brain axis bidirectionally regulates sleep physiology through various pathways [139].

Addiction disorders

Metabolites of gut microbiota have an essential role in the substance abuse disorders including SCFAs and bile acids. Vagal nerve stimulation, brain-derived neurotropic factor, and gut epithelial barrier dysfunction with bacterial translocation represent other factors that link microbiota with addiction [140].

Alcohol

Initial gut microbiome studies in substance abuse focused heavily on alcohol use. Chronic alcoholics exhibit reduced gut microbiome diversity and alter composition compared to healthy controls, with fewer beneficial Firmicutes (Lactobacilli, Enterococci) and Actinobacteria (Bifidobacteria) [141]. Acute alcohol exposure may temporarily disrupt intestinal permeability, enabling bacterial products to enter circulation [142]. This leakage is linked to increased depression and cravings in the recovering alcoholics [143]. In a meta-analysis, dopamine, GABA, serotonin, and norepinephrine were found to be the main neurotransmitters upregulated in the presence of alcohol. Alcohol-induced alteration of microbiota can have adverse effect on the brain function and play a vital role in addiction and alcohol dependence [144].

CNS stimulants

Cocaine induces upregulation of the proinflammatory mediators in the GI tract along with a compromise of mucosal barrier integrity [145]. Cocaine use is independently associated with intestinal dysbiosis and increased Bacteroidetes [146] and alteration of Verrucomicrobia and Firmicutes [147]. Furthermore, patients with cocaine use disorder showed marked dysbiosis of both foecal and oral microbiota composition and function [148]. Opioid

use correlates with altered gut microbiome composition in some studies [149–151] but not in others [152]. Confounding factors like polysubstance abuse require further research. However, opioids appear to change gut microbial communities and function in ways that may impact the drug effects [140].

Anxiety

No published research has examined the relationship between gastrointestinal microbiota and any specific anxiety disorder. Among the various anxiety disorders, obsessive-compulsive disorder has exhibited the strongest correlation with infection, particularly respiratory tract infection caused by group A *beta-hemolytic streptococcus* [153], while there is a lack of research examining the efficacy of probiotics in patients with obsessive-compulsive disorder. A study on rodents indicates that *L. rhamnosus* may have some potential impact [154]. Lyte et al. discovered that anxiety-like behaviour in rodents was induced by subclinical concentrations of the pathogen *Campylobacter jejuni* administered orally via gavage. These doses failed to elicit an overt immune response. Involvement of brainstem regions, including the nucleus tractus solitarius and lateral parabrachial nucleus, in the processing that generates autonomic, neuroendocrine, and behavioural responses was also observed [155]. Bruch examined the Medical Expenditure Panel Survey to determine prospectively whether intestinal infection is associated with the future onset of an anxiety disorder and compelling evidence supporting a correlation between intestinal infection and the subsequent onset of anxiety [156].

Role of microbiota as a treatment option for psychiatric illness

Diet

Food has a substantial impact on the gut microbiota, and studies have shown that making dietary modifications in a short period of time (24 h) can modify the structure of the intestinal microbiota system [157], which could be offered as an adjuvant antidepressant medication. It has been demonstrated that specific dietary components can maintain the gut microbiota's structural homeostasis; this effect is believed to have clinical implications. Patients can alleviate the influence of minor symptoms by reducing psychological resistance to treatment through nutritional relief. Prebiotics are nondigestible fibres that promote the growth of beneficial gut microbes by being partially digested in the gastrointestinal tract [42].

Prebiotics

Prebiotics in diet, such as inulin, oligofructose, fructooligosaccharide (FOS), and galacto-oligosaccharide (GOS),

could influence the intestinal microbiota ecosystem structure, which is drastically diminished in patients with depression [158]. Tarr's experiment in 2015 proved that the oligosaccharides 3-sialyllactose (3SL) or 6-sialyllactose (6SL) in human breast milk inhibit the development of anxiety [159]. Healthy diet like the Mediterranean diet which includes high levels of plant compounds, vitamins, minerals, PUFAs, and dietary fibres is recommended for patients who suffer depression [34].

Probiotics and psychobiotic

People usually support probiotics' antidepressant and anti-anxiety properties, but additional confirmation is still needed due to inaccuracy and a lack of clinical tables [43]. Schnorr and Bachner administered a combination of psychotherapy and dietary intervention to an apprehensive patient. Instead of hyperglycaemic diets, they incorporated meals that were abundant in probiotics. The results indicated that this therapeutic regimen decreased the prevalence of unfavourable microorganisms (e.g. *Clostridium*), increased the abundance of beneficial microorganisms (e.g. *Lactobacillus*), and improved anxiety and insomnia. Additionally, the drug regimen altered the composition and diversity of bacteria [160].

Variable probiotics possess potent stress-modulating and anxiolytic effects which make those probiotics to be promising living psychobiotics for alleviating psychological disorders. They act by maintaining the intestinal homeostasis, improving mucosal and systemic immunity, and regulating the metabolism of gut microbiota. The main microbial genera with psychobiotic characteristics are *Lactobacillus*, *Lactococcus*, and *Bifidobacterium* [161].

Aberrant intestinal microbiota diminishes the stability of the gastrointestinal barrier, allowing increased entry of lipopolysaccharides (LPS) into the body. This, in turn, triggers systemic inflammation and a stress response [162]. However, probiotic medication can effectively prevent damage to the intestinal barrier and enhance its function through various mechanisms, ultimately reducing the reactivity of the HPA axis to stress [163]. Probiotics such as *Lactobacillus rhamnosus* can regulate plasma corticosterone levels induced by excitation and alleviate depression by influencing hormones released by the vagus nerve and hippocampus, including BDNF and oxytocin [164]. Also, the vagal nerve regulates the activity of *Bifidobacterium infantis*, which is associated with hormones including acetylcholine and corticosterone [7]. It is important to note that different probiotic strains may affect individuals differently. For instance, a study revealed that the ingestion of *Lactobacillus casei* did not significantly improve health in all patients when they were in a healthy state [165]. Notably, the effect of

probiotics proved in experiencing anxiety or depression [165]. Conversely, in another investigation, healthy subjects consuming a meal containing *L. helveticus* and *B. longum* for 30 days reported improved stress states and negative mood regulation. Daily intake of *L. casei* strain Shirota has been shown to enhance gut microbiota composition and function, potentially reducing stress exposure symptoms in healthy participants [166].

In addressing treatment-resistant depression (TRD), Bamling et al. employed a unique combination of antidepressant treatment with probiotics, magnesium, and selective serotonin reuptake inhibitors (SSRIs), resulting in a significant improvement in depressive symptoms [167]. Additionally, *Lactobacillus plantarum* JYLP-326 was reported to alleviate anxiety, depression, and insomnia in college students experiencing test anxiety [168]. However, the efficacy of probiotics in treating gastrointestinal or behavioural symptoms in children with autism spectrum disorder (ASD) is limited [169].

Synbiotic

Synbiotics, a combination of prebiotics and probiotics, have been found to alleviate depression in patients undergoing haemodialysis. The supplementation of synbiotics was associated with increased serum levels of BDNF in a subgroup of patients with depression [170, 171].

Engineered bacteria

Engineered bacteria, such as L-4-chlorokynurenine (L-4-Cl-KYn) expressed by marine bacteria, have been utilized to treat depression. Combined with the strain's native enzymes, it enhances the therapeutic effect [172]. Targeting peptide release in the intestines could be a promising method for integrating with future psychological discoveries, focusing on peptide-mediated immune responses, enhanced vagal signalling, or regulation of neuropeptide expression in specific brain regions. However, intestinal peptides face practical limitations, including a brief half-life and slow traversal of the blood-brain barrier [173]. Modified strains with targeted peptide chemistry modifications may enhance the efficacy of intestinal peptides, and ongoing efforts aim to improve both modified peptide chain sequences and strain selection [174].

Faecal microbiota transplantation (FMT)

FMT involves transferring faecal microorganisms from a donor to a recipient. While FMT has been effective in treating microbial structural abnormalities and depression, it can induce anxiety, depressed behaviours, and stress responses in healthy individuals.

Nevertheless, FMT has demonstrated positive outcomes in treating microbial structural abnormalities [175] and depression [176, 177] and reprogramming the

host's metabolism [178]. Previous study demonstrated that FMT could regulate serotonin levels, reduce gut epithelial validation response, and control inflammatory response. Additionally, it can affect the variety and ecosystem structure of colon microbiota [179]. FMT has also exhibited antidepressant effects on depression induced by chronic, unpredictable mild stress in rats, impacting various neurotransmitters, inflammatory factors, neurotrophic factors, and glucagon-like peptides [180]. In patients with major depression, oral frozen FMT capsules, used as an add-on therapy, significantly improved depressive symptoms after 4 weeks of treatment [181].

Irritable bowel syndrome (IBS), a gastrointestinal functional disorder, is a common consequence of depression [182]. FMT has been incorporated into typical treatment programmes for IBS, showing significant efficacy with remission rates of up to 89% in treated patients [183]. Although some negative consequences have been observed after FMT treatment due to alterations in the intestinal microbiota [184], most of these effects are modest [185] or reversible [184].

Conclusions

In conclusion, the gut microbiota plays a fundamental role in brain development, with its composition evolving from birth to ageing. Factors such as diet, stress, disrupted circadian rhythms, environmental and occupational factors, and even COVID-19 can influence the microbiota composition, leading to dysbiosis implicated in various diseases, including those affecting the central nervous system. Gut-brain axis and microbiota dysbiosis could have a major role in pathogenesis of various mental disorders. As a result, the use of psychobiotics and faecal microbiota transplantation has emerged as a potential significant aspect of managing psychiatric diseases. Further research is still needed to address the exact causal link between certain microbial changes and various psychiatric disorders with further implication on the management for these conditions.

Abbreviations

| | |
|-------|--|
| CNS | The central nervous system |
| PYY | Peptide YY |
| 5-HT | Serotonin |
| GF | Germ-free |
| HPA | The hypothalamic-pituitary-adrenal axis |
| BDNF | Brain-derived neurotrophic factor |
| CS | Caesarean section |
| VD | Vaginally delivered |
| ASD | Autism spectrum disorder |
| PACS | Post-acute COVID-19 syndrome |
| CRH | Corticotropin-releasing hormone |
| AVP | Arginine vasopressin |
| PUFAs | Polyunsaturated fatty acids |
| PTSD | Posttraumatic stress disorder |
| ADHD | Attention-deficit hyperactivity disorder |

| | |
|------------|-----------------------------------|
| VOC | Volatile organic compounds |
| SCFAs | Short-chain fatty acids |
| BD | Bipolar disorder |
| MDD | Major depressive disorder |
| EMR | Endogenous melatonin reduction |
| TRD | Treatment-resistant depression |
| FMT | Faecal microbiota transplantation |
| IBS | Irritable bowel syndrome |
| L-4-Cl-Kyn | L-4-chlorokynurenine |

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