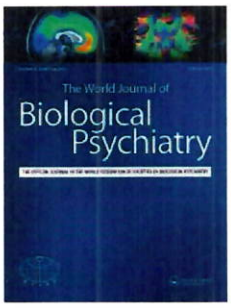

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REVIEW ARTICLE

Assessing the relationship of gut microbiota with neurological, psychiatric, and neurodegenerative disorders: a narrative review

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ABSTRACT

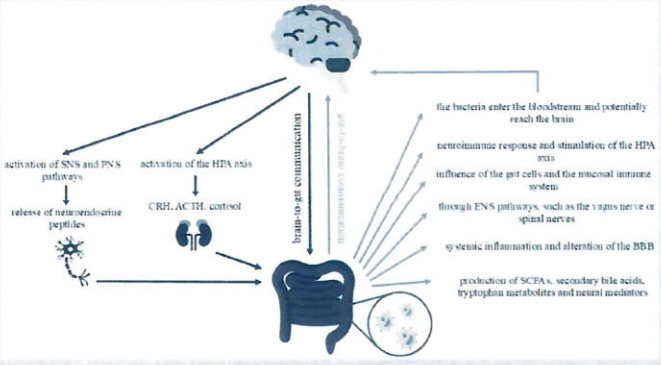
Objectives: The gut–brain axis is a bidirectional communication network regulated by the immune, nervous, and endocrine systems, microbial metabolites, and environmental factors such as diet, stress, circadian rhythm, and drugs/chemicals. This review aims to examine current literature on the link between gut microbiota dysbiosis and major brain disorders, and to explore strategies for improving patient outcomes.

Methods: This narrative (non-systematic) review investigated the association between gut microbiota dysbiosis and psychiatric (schizophrenia, major depressive disorder, bipolar disorder, eating disorders), neurological (autism spectrum disorder, attention deficit hyperactivity disorder, epilepsy, migraine), and neurodegenerative disorders (Parkinson's disease, Alzheimer's disease, multiple sclerosis). It also considered potential microbiota- and neuroprotective interventions.

Results: The existing body of evidence consistently links gut dysbiosis with neuropsychiatric and neurodegenerative conditions through mechanisms including inflammation, impaired intestinal barriers, microbial production of neurotransmitters or toxins, and accumulation of α-synuclein or amyloid affecting neurogenesis and myelination. Balanced dietary patterns and the use of probiotics, prebiotics, or fermented foods are associated with healthier gut microbiota and improved neurological function.

Conclusions: Further research is needed to clarify whether gut dysbiosis causes or contributes to these disorders, and to develop evidence-based, gut-focused practical recommendations for their prevention and management.

GRAPHICAL ABSTRACT



List of abbreviations: AD: Alzheimer's Disease; ADHD: Attention-Deficit Hyperactivity Disorder; AN: Anorexia Nervosa; ANS: Autonomous Nervous System; ASD: Autism spectrum disorder; BD: Bipolar Disorder; CNS: Central Nervous System; ENS: Enteric Nervous System; HPA: Hypothalamic-Pituitary-Adrenal; GABA: Gamma-aminobutyric acid; LPS: Lipopolysaccharide; MCI: Mild cognitive impairment; MDD: Major Depressive Disorder; MS: Multiple Sclerosis; SCFAs: Short-chain-fatty-acids

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1. Introduction

The human microbiota is a complex ecosystem of microorganisms living in and on the human body (Shafquat et al. 2014). While the existence of those microorganisms is known since the birth of microbiology, only recently, in the past twenty years, have we started to learn more about the complex ecologies they form (Shafquat et al. 2014; Balskus 2018).

Humans have co-evolved with their microbiota, forming symbiotic relationships (Lloyd-Price et al. 2016). The interactions between the host and their endogenous microorganisms start with birth (Ahrodia et al. 2022). The microbiota influences the overall human health and physiology, including digestion, immunity, and disease resistance (Shafquat et al. 2014; Lloyd-Price et al. 2016; Ahrodia et al. 2022).

The Human Microbiome Project initially aimed to identify a 'core' microbiome shared by all healthy individuals (Shafquat et al. 2014); however, the human microbiome was proved to be highly diverse (Ahrodia et al. 2022). Early findings revealed that individual differences in the microbiome are significant, even among closely related people (Shafquat et al. 2014).

A healthy microbiota is characterised by its resilience to external and internal changes, and its core is defined by the total of its functional capabilities (metabolic and molecular) rather than the specific microbial species that compose it (Lloyd-Price et al. 2016). The overall microbial ecosystem balance is called eubiosis and is based on the healthy symbiotic interactions between the microbiota and the human body (Iebba et al. 2016). On the other side, dysbiosis, an imbalance in the host-microbiota relationship, has been linked to various health problems (Iebba et al. 2016; Milani et al. 2017).

2. The gut microbiota

The gut microbiota is a complex community of microorganisms formed in the gut (Milani et al. 2017). It includes both indigenous (autochthonous) and transient (allochthonous) microorganisms, and remains relatively stable throughout life (Milani et al. 2017). While some parts of the gut microbiota are consistent, many vary based on factors such as gender (microgenderome), age, environment, culture, and health conditions (Milani et al. 2017; Vemuri et al. 2019; Snigdha et al. 2022).

The growing existing body of evidence suggests that bacteria may be present in the placenta, umbilical cord, and amniotic fluid during pregnancy (Milani et al. 2017). This could mean that the microbial colonisation of fetus' gut may start even before birth. The way of delivery also affects the composition of the gut microbiota (Biasucci et al. 2010; Dominguez-Bello et al. 2010; Milani et al. 2017). It has been also found that breastfed infants have higher levels of beneficial bacteria compared to formula-fed infants (Schneider et al. 2024). Moreover, the establishment and interactive development of the early gut microbiota are thought to be (at least partially) modulated by specific compounds present in human milk (Milani et al. 2017).

Most importantly, the gut microbiota are influenced by various environmental factors, including pH, oxygen levels, nutrients, and temperature (Milani et al. 2017). Other external factors include diet, lifestyle, antibiotics and other drugs, hygiene, the genetics and immune status of the host (Sommer and Bäckhed 2013). The total of these factors create niches for different microbial populations to thrive and interact with their environment (Sommer and Bäckhed 2013; Ahrodia et al. 2022).

The gut microbiota play a crucial role in producing various metabolites, such as fatty acids, neurotransmitters, vitamins, and hormones (Silva et al. 2020; Anand et al. 2022). They break down undigested complex dietary fibres and produce essential bioactive metabolic products, known as gut-derived metabolites, that include short-chain fatty acids (SCFAs), long-chain fatty acids, branched-chain amino acids, trimethylamine-N-oxide, lipopolysaccharide (LPS), bile acids, and catecholamines (Anand et al. 2022).

The most important functions of the gut microbiota, *via* its metabolites, include the modulation of the immune and nervous system, the prevention of excessive inflammation, the contribution to cell differentiation, organ development and morphogenesis, the assistance in metabolism and the protection against pathogens and harmful bacteria (Sommer and Bäckhed 2013; Milani et al. 2017; Adak and Khan 2019).

3. Microbiota-gut-brain axis

Many studies have revealed the concept of a microbiota-gut-brain axis mediating bidirectional communication between the gut, its microbiota, and the nervous system (Osadchiy et al. 2019). Indeed, gut microbiota communicate with the brain either directly or indirectly in a complex and multidimensional manner *via* neural, immune, and entero-endocrine signalling pathways, forming the microbiota-gut-brain axis (Dinan and Cryan 2017; Malagelada 2020). For the means of simplicity, we will use the term 'gut-brain axis' throughout the manuscript including the 'microbiota-gut-brain axis' perspective.

The immune system influences the brain-gut axis by changing cytokine production. The nervous system communicates with the immune system to maintain balance *via* the autonomous nervous system (ANS), including the stimulation of the vagus nerve and the enteric nervous system (ENS) (Dinan and Cryan 2017). The endocrine system influences the axis *via* the activation of the hypothalamic–pituitary–adrenal (HPA) axis and is associated with the production and secretion of CRH, ACTH and cortisol, which can modulate the intestinal immune and barrier functions. Any disruptions in those interactions early in life can have long-lasting effects on the cognitive and behavioural well-being of the host (Dinan and Cryan 2017).

3.1. Gut-to-brain communication

The gut signals the brain (bottom-to-top approach) by modulating higher cognitive and behavioural functions, directly or indirectly (Anand et al. 2022). The primary way of gut-to-brain indirect communication is through the substances the microbes produce, such as SCFAs, secondary bile acids, and tryptophan metabolites and neural mediators. Thereby, they affect neuroendocrine and immune responses including microglial activity and release of cytokines (Ghadiri et al. 2022). There are some bacterial intermediates that influence directly the gut cells (enteroendocrine cells, enterochromaffin cells) and the mucosal immune system to propagate bottom-to-top signalling, while others can enter the bloodstream and potentially reach the brain, by crossing the blood-brain barrier (Osadchiy et al. 2019).

Other potential ways of gut-to-brain interaction include: i) directly through nerve pathways, such as the stimulation of the vagus nerve or spinal nerves and the enteric nervous system (ENS) (Osadchiy et al. 2019), ii) neuroimmune response and stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, iii) systemic inflammation, and iv) alteration of the blood-brain barrier's (and the gut mucosal barrier's permeability) (Anand et al. 2022; Ghadiri et al. 2022).

3.2. Brain-to-gut communication

At the same time, the central nervous system (CNS) can modulate the gut microbiota (top-to-bottom approach) through sympathetic and parasympathetic nerve pathways and the release of neuroendocrine peptides (Spekker and Nagy-Grócz 2023). The brain signals the gut by regulating the sensory, motor, and secretory functions of the gastrointestinal tract, and *via* the HPA axis, in the presence of stressful stimuli (Anand et al. 2022). Catecholamines, influenced by stress, are often involved in the direct signalling process. Additionally, both the CNS and the autonomous nervous system (ANS) can indirectly affect the microbiota by altering the gut environment and physiology (Osadchiy et al. 2019).

3.3. Factors affecting the gut-brain axis

Some other factors affecting the gut-brain axis include:

1. The long-term and broad-spectrum antibiotic use, which changes the composition of the gut microbiota, and the levels of neuromodulators communicating along the gut–brain axis (tryptophan, kynurenine, serotonin metabolites, vasopressin, and oxytocin), leading to altered signalling and, thus, changes in anxiety, depression, memory, and neurocognition (Desbonnet et al. 2015; Lurie et al. 2015; Osadchiy et al. 2019).
2. Specific diet patterns (e.g. a low-fibre diet), which may impact the brain structure, specifically the white matter architecture (Sonnenburg et al. 2016; Ong et al. 2018).
3. Stressful stimuli, which can significantly affect the gut microbiota via the HPA axis or by increasing LPS levels, and intestinal permeability (Galley et al. 2014; Osadchiy et al. 2019; Anand et al. 2022; Góralczyk-Bińkowska et al. 2022).
4. The circadian rhythm, any disruptions of which particularly in adverse nutritional environments may contribute to pathological microbial glucose metabolism (Zhou et al. 2019).
5. Occupational and environmental exposure to chemicals, physical agents, and biological hazards in the workplace, which might adversely affect the gut microbiota (Mucci et al. 2022).

4. Gut microbiota dysbiosis and its link with psychiatric, neurological and neurodegenerative disorders

The microbiota-gut-brain axis mediates the effects of both genetic and environmental factors on brain development and function (Patel et al. 2025). Dysfunctional gut-brain signalling has been linked to various neurodegenerative, neurodevelopmental, and neuropsychiatric disorders (Wang et al. 2021; Anand et al. 2022). Specific gut bacteria and the produced

neurotransmitters like gamma-aminobutyric acid (GABA) and serotonin may play a significant role in neuropsychiatric disorders (Zhuang et al. 2020). Chronic gut dysbiosis and early-life disturbances in the gut microbiota can overstimulate the HPA axis and the neuroimmune system, and, thereby, lead to dysfunctional signal transduction, inflammation, increased oxidative stress, mitochondrial dysfunction, and neuronal death (Anand et al. 2022). Moreover, emerging evidence suggests the microbiota actively influences CNS development, with alterations having an impact on neuroplasticity, cognition and behaviour (Patel et al. 2025).

Recent research points out a link between disruptions in synaptic pruning and the development of psychiatric symptoms when the gut-brain axis is impaired due to gut dysbiosis (Anand et al. 2022). Patterns of dysbiosis have been observed in various disorders, such as schizophrenia, major depressive disorder (MDD), bipolar disorder (BD), autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), epilepsy, migraine, in neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and in mental health conditions, such as eating disorders (Socała et al. 2021; Góralczyk-Bińkowska et al. 2022; Schneider et al. 2024). This might be due to the underlying neurological disorder per se or due to the subsequent psychological stress and inflammation associated with those diseases (Socała et al. 2021). Disease-specific patterns of changes in the diversity and composition of the gut microbiota are briefly presented below.

According to a meta-analysis published in 2021 (Nikolova et al. 2021), there is no evidence for disorder specificity in the patterns of gut dysbiosis. It is suggested that this may reflect specific population characteristics (e.g. depression subtype). Instead, the findings indicate that certain disorders with overlapping pathophysiology (e.g. psychosis and schizophrenia, BD, anxiety, and MDD) share similar patterns of microbial changes.

Interestingly, gut microbiota has played a significant role in neuropsychiatric symptoms during COVID-19 (Zeng and Tang 2024). In relation to COVID-19, potential changes in gut bacterial composition and their long-term effects were observed, revealing patterns of dysbiosis. Particularly, Zeng Z. et al. suggested a certain gut microbiota species that could possibly influence both COVID-19 and psychiatric disorders, indicating potential shared pathogenic pathways (Zeng and Tang 2024). This observation highlights the potential significance of the gut microbiota in understanding and preventing neuropsychiatric symptoms during major epidemic diseases.

4.1. Gut dysbiosis and psychiatric conditions

4.1.1. Schizophrenia

Schizophrenia patients often report gastrointestinal symptoms (e.g. gastritis, enteritis and colitis) (Severance et al. 2015; Hemmings 2004). Studies have shown differences in the composition, diversity and metabolic pathways of the gut microbiota in individuals with schizophrenia, linked to changes in anxiety, memory, cognition, and locomotor activity (Golofast and Vales 2020). This has been confirmed by histological findings as well, such as the presence of defective intestinal barrier wall (Castro-Nallar et al. 2015; Anand et al. 2022). Interestingly, malnourishment during pregnancy or infancy, through underfeeding or overfeeding, elevates the risk of schizophrenia for the newborn, as it can trigger inflammation, potentially mediated by the gut microbiota (Schneider et al. 2024). Another study revealed that faecal microbiota transplantation from schizophrenia patients induces schizophrenia-like behaviours in germ-free mice and alters the lipid metabolism in their serum and hippocampus (Zheng et al. 2019).

4.1.2. Major depressive disorder

Depression has been linked with hyperactivation or deregulation of the HPA axis, dysregulation of the neuro-immunological and neuro-transmitter signalling pathways, deficiency of tryptophan and GABA metabolism, reduced SCFAs production, and impaired intestinal barrier integrity, all potentially associated with gut dysbiosis (Łoniewski et al. 2021; Anand et al. 2022). Evidence indicates that gut and brain peptide secretion exhibits considerable anatomical and functional overlap, revealing shared downstream effects on neural circuits implicated in the pathophysiology of depression (Patel et al. 2025). Additionally, it has been shown that the gut microbiota differs significantly when comparing patients with MDD and healthy controls (Sanada et al. 2020; Knudsen et al. 2021). Indeed, depressed individuals exhibit a reduced diversity and abundance of gut bacteria, which is correlated with elevated levels of proinflammatory factors, cortisol, and alterations in tryptophan metabolism (Wieërs et al. 2019). The gut microbiota modulates the expression of brain-derived neurotrophic factor as well, a critical regulator of neuroplasticity, with reduced levels linked to mood dysregulation and increased depression risk (Patel et al. 2025). MDD patients also exhibit higher levels of serum antibodies due to the excessive presence of LPS from gram-negative enterobacteria, than general population controls (Maes et al. 2008; Anand et al. 2022). MDD patients are consistently

found to exhibit enriched pro-inflammatory bacteria and depleted anti-inflammatory bacteria, a fact that supports the inflammatory hypothesis of depression (Patel et al. 2025). The transplantation of gut microbiota from depressed patients to germ-free rats resulted in the development of depression-like behaviours and physiological changes (Wieërs et al. 2019).

The interplay of the gut microbiota and blood metabolome, may play a role in lipid metabolism in those patients (Amin et al. 2023). It should be noticed that emotional eating, a coping mechanism used by some individuals with anxiety and depression, can negatively alter the gut microbiota (Schneider et al. 2024). Both hyperphagia and hypophagia can result in malnutrition or deprivation of gut microbiota, which may dysregulate the gut-brain axis and further worsen psychological symptoms.

4.1.3. Bipolar disorder

BD is assumed to be correlated with gut dysbiosis (Lucidi et al. 2021; Obi-Azuike et al. 2023). This is partly supported by the fact that antibiotic therapy has been associated with acute manic episodes in patients with BD (Yolken et al. 2016). Specifically, the microbiota through the Toll-like receptors are involved in regulating the innate immune response at the CNS level (Lucidi et al. 2021). They recognise specific constituents of Gram-positive bacteria and Gram-negative LPS, and their activation can lead to the production of pro-inflammatory cytokines that can cross the blood-brain barrier. Another potential mechanism involved in BD pathogenesis might be the microbiota's influence on synaptic pruning, a process that occurs during brain development (Lucidi et al. 2021). Gut microbiota interfere with microglial cells in the synaptic pruning process during critical periods of development, having a direct effect on neural circuits.

4.1.4. Eating disorders

Eating disorders, including anorexia nervosa, bulimia nervosa and binge-eating disorder, are defined by disruptions in eating behaviours (Schneider et al. 2024). Anorexia nervosa (AN) is the most researched disorder within the context of the gut microbiota. Faecal microbiota transplantation from human donors with anorexia nervosa to germ-free mice induces AN-like behaviour, such as slower weight gain over time and altered expression of hypothalamic genes related to appetite and energy expenditure. It had been speculated that the microbiota-AN relationship is mediated by the elevation of bacteria (such as Methanobevibacter smithii) and metabolites associated with food restriction (Schneider et al. 2024). Alterations of the gut microbiota attributed to disordered eating habits can subsequently lead to disease progression, and may play a primary role in the different stages of the disorder.

4.2. Gut dysbiosis and neurological conditions

4.2.1. Autism spectrum disorders

Almost half of children with autism spectrum disorders (ASD) report gastrointestinal symptoms (altered bowel habits, constipation, colic, gastroesophageal reflux, diarrhoea, bloating, chronic abdominal pain) often in line with the severity of their behavioural and emotional symptoms (Holingue et al. 2018; Anand et al. 2022). The existing body of evidence reveals that the gut microbiota dysbiosis in ASD is rather common (Fattorusso et al. 2019).

However, there is no single distinctive profile of altered gut microbiota composition in patients with ASD. A possible reason may be the lack of homogeneity in terms of age, diet, pharmacological treatment, geographic area (regionality), comorbidities, and the severity of neuro-behavioural and gastrointestinal symptoms among the ASD patients enrolled. Children with ASD also exhibit general fear and/or rejection towards new or unfamiliar foods, alongside consumption of fewer fruits and vegetables, but greater intake of high-carbohydrate and/or high-fat foods, which rationalised the impact of host nutritional intake on their gut microbiota (Yap et al. 2021; Schneider et al. 2024). Food selectivity is related to avoidant/restrictive food intake disorder, which is likely underdiagnosed, despite affecting over 20% of children with ASD (Koomar et al. 2021; Yap et al. 2021).

The mechanisms underlying gut dysbiosis in ASD appear to be: i) the increased intestinal permeability that allows bacterial products like LPS to enter the bloodstream, ii) the inflammation-related disruption of serotonin synthesis that leads to functional intestinal problems and reduced brain serotonin levels, and iii) alterations in the myelin-related genes of the prefrontal cortex (in which the gut microbiota is involved) may also be linked to ASD-like behaviours (Kraneveld et al. 2016; Galvez-Contreras et al. 2020).

4.2.2. Attention deficit hyperactivity disorder

Recent research supports that imbalances in the intestinal microbiota are involved in poor brain development and neurogenesis in patients with ADHD (Kalenik et al. 2021). Indeed, patients with ADHD appear to have gut microbiota alterations compared to healthy controls (Wang et al. 2022). Additionally, chronic intake

of food, which can cause inflammation and reduce dopamine activity (such as sugar, soda, candy), has been linked to an increased prevalence of ADHD diagnosis, as well (Schneider et al. 2024). The gut microbiota may interfere in the catecholaminergic neurotransmission system and also exacerbate the mechanisms of neuroinflammation and oxidative stress, already present in ADHD (Checa-Ros et al. 2021).

4.2.3. Epilepsy

The role of the gut-brain axis in epilepsy cannot be ignored (Ding et al. 2021). Epilepsy is often linked with imbalance of neurotransmitters, in areas of the brain that cause seizures (hypoactivity of GABA and serotonin, and hyperactivity of glutamate, dopamine and norepinephrine) (Werner and Coveñas 2017). The gut microbiota can affect neurotransmitters, both by producing them directly and by influencing the production of neurotransmitters by other cells in the digestive system (Ding et al. 2021). The gut microbiota can also affect the function of the hypothalamus by changing circulating cytokine levels or other pathways, thereby, regulating the HPA axis (de Weerth 2017), which can be a trigger factor for seizures, related to cortisol level increases (Cano-López and González-Bono 2019; Ding et al. 2021).

Moreover, the vagus nerve seems to contribute to the gut-brain communication and to have potential involvement in the pathogenesis of some epilepsy cases (Ding et al. 2021). Ressler et al. reported that electrical stimulation of vagal afferent fibres can modify brain concentrations of serotonin, GABA, and glutamate, thus, explaining its effectiveness in epilepsy (George et al. 2007; Ressler and Mayberg 2007). The vagus nerve goes through all intestinal layers, except the epithelial one, so it cannot directly interact with the gut microbiota. However, Kaelberer et al. found that enteroendocrine cells (named neuropod cells) can detect signals released from the luminal microbiota through different receptors. These cells can synapse with vagal neurons to transduce gut luminal signals, connecting the intestinal lumen to the brainstem using glutamate as a neurotransmitter (Kaelberer et al. 2018; Ding et al. 2021).

4.2.4. Migraine

In recent years, accumulating evidence demonstrate that gut microbiota might play an important role in the development and maintenance of migraine (Crawford et al. 2022). Migraine patients often experience nausea and vomiting, and a higher prevalence of gastrointestinal disorders (such as high reflux, diarrhoea, constipation) has been identified in individuals with frequent headaches (Aamodt et al. 2008; Cámara-Lemarroy et al. 2016). Recent research has shed light on differences in gut microbiota composition between migraine sufferers and healthy controls, in both adult and child populations (Crawford et al. 2022; He et al. 2023). This interaction might be influenced by multiple factors such as inflammatory mediators, neuropeptides and serotonin pathway, stress hormones and nutritional substances (Arzani et al. 2020). Specifically, the glutamatergic neurotransmission may be a link between migraine and the microbiota (Spekker and Nagy-Grócz 2023), while higher levels of bacteria that reduce nitrates and nitrites have been observed in migraine patients, and, thus, have a potential role in triggering migraines (Gonzalez et al. 2016).

4.3. Gut dysbiosis and neurodegenerative disorders

4.3.1. Parkinson's disease

Preclinical research suggests that abnormal aggregation of α-synuclein and spreading of pathology between the gut, brainstem, and higher brain regions probably underlie the development and progression of PD (Morris et al. 2024). Indeed, gastrointestinal symptoms, gut microbiota dysbiosis and alterations of the ENS accompany the disease and may precede the typical motor symptoms of PD (Qian et al. 2018; Romano et al. 2021). Gut microbiota dysbiosis appears even earlier than the α-synuclein formation in animal brains (Qian et al. 2018). The causes behind PD-related microbiota dysbiosis are maladaptive immuneresponses triggered in the gut, pathologic interaction with the ENS and the CNS, altered production of neurotransmitters like glutamate and GABA, and inflammatory and proinflammatory reactions that may contribute to the misfolding of α-synuclein and the development of PD pathology (Keshavarzian et al. 2015; Romano et al. 2021). PD patients exhibit distinct gut microbiota profiles, characterised by changes in pro-inflammatory pathways and reduced biosynthesis of neurotransmitter precursors (Pietrucci et al. 2019; Romano et al. 2021). Some bacteria may be correlated with disease duration, severity, medication and non-motor symptoms (Qian et al. 2018).

4.3.2. Alzheimer's disease

AD and its prodromal-predementia stage of mild cognitive impairment (MCI) are both marked by significant gut microbiota perturbations, suggesting the early involvement of gut-brain axis in disease progression (Li et al. 2019; Jemimah et al. 2023). Those patients exhibit an increase in pro-inflammatory bacteria and a

decrease in potentially protective species (Guo et al. 2021). The degree of gut dysbiosis worsens as the disease progresses from MCI to AD (Guo et al. 2021).

Gut dysbiosis can lead to neurodegeneration through secretion of LPS, immune activation, systemic inflammation, and blood-brain barrier and gut barrier impairment, mediated by microbiota metabolites like SCFAs and proinflammatory cytokines (Braniste et al. 2014; Li et al. 2019; Kesika et al. 2021; Jemimah et al. 2023). It also promotes neuroinflammation, neuronal injury, and ultimately leads to neuronal death in AD (Kesika et al. 2021). Additionally, certain bacteria can produce amyloid fibres, which can contribute to AD pathogenesis (Li et al. 2019). Not only ageing but also dietary habits can influence gut microbiota composition and contribute to AD risk; thus, targeting gut microbiota through dietary interventions may offer potential benefits for cognitive health (Kowalski and Mulak 2019; Ghosh et al. 2020; Schneider et al. 2024).

4.3.3. Multiple sclerosis

The gut microbiota may be one unidentified environmental risk factor in the development of MS, as it can influence the immune system and the progression of the disease (Preiningerova et al. 2022). Research suggests that gut dysbiosis can contribute to a shift in proinflammatory factors and, thereby, to inflammation in the CNS (Ghadiri et al. 2022; Preiningerova et al. 2022). Gut microbiota may contribute to MS pathology by decreasing SCFAs (Ghadiri et al. 2022). Additionally, the gut microbiota has been linked to cognitive function, one of the key areas affected by MS (Ghadiri et al. 2022). Indeed, in patients with MS, it has been found that the composition of their microbiota is relatively less diverse that of healthy individuals (Preiningerova et al. 2022). Whereas some microbiota alterations are shared in relapsing and progressive MS, Cox et al. identified unique bacteria associated with progressive MS and clinical measures of disease (Cox et al. 2021).

5. How to maintain a healthy microbiota-gut-brain axis

Given the fact that individuals with neuropsychiatric disorders tend to live about 20 years less than the general population, primary and secondary prevention interventions could substantially improve their prognostic course (Firth et al. 2019; Berding et al. 2021). The term 'psychobiotics' has been introduced to describe external factors that may influence the gut microbiota, such as probiotics, prebiotics, and diet, and potentially have positive effects on mental health (Berding et al. 2021). The specific effect of each of those factors is briefly described below.

5.1. Diet

A complex relationship exists between diet, gut microbiota, and brain health (Berding et al. 2021; Schneider et al. 2024). Dietary habits can significantly alter the composition and function of the gut microbiota whilst affecting the metabolic activity of gut bacteria at a (meta-) genomic level (Albenberg and Wu 2014). It is supported that poor dietary habits contribute to the accelerating trend of neuropsychiatric disorders, while healthy dietary intake supports mood and cognitive performance (Schneider et al. 2024). However, individual responses to dietary changes can vary due to differences in gut microbiota composition (Berding et al. 2021).

The consumption of a fibre-rich diet (i.e. high consumption of fruits, vegetables, whole grains) is widely recognised to foster an increase in bacterial diversity and stimulate the proliferation of beneficial gut microbiota (Berding et al. 2021; Ioniță-Mîndrican et al. 2022). Soluble, fermentable fibre can increase microbial enzymatic capacity to degrade complex carbohydrates and produce health-promoting SCFAs (acetate, propionate, butyrate) (Berding et al. 2021).

Omega-3 polyunsaturated fatty acids (α-linolenic acid, stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) have been shown to promote an eubiotic state as well, characterised by an increase in beneficial bifidobacteria and a decrease in enterobacteria, which facilitates an anti-inflammatory environment through the production of SCFAs and suppression of endotoxemia (Shahidi and Ambigaipalan 2018; Berding et al. 2021). Robertson et al. suggest that cognitive, anxiety, and social behaviours are strongly influenced by the availability of *n*–3 polyunsaturated fatty acids during foetal development and throughout life (Robertson et al. 2017).

Polyphenols are a class of bioactive compounds with phenolic structures (found in fruits, vegetables, cocoa, spices, whole grains, nuts, and extra virgin olive oil, red wine, coffee, green tea) (Neveu et al. 2010; Guo et al. 2023) which have been shown to have neuroprotective effects on the grounds of their anti-inflammatory and antioxidant properties (Berding et al. 2021). They have been linked to improved cognitive function, reduced stress hormones and pro-inflammatory cytokines, and alleviated depression-like behaviours (Dueñas et al. 2015; Berding et al. 2021).

Additionally, the beneficial effects of fruits and vegetables are not only attributed to their richness in polyphenols, but also to their microbiota-accessible

carbohydrates (Han and Xiao 2020). Thus, gut microbiota can transform the components of fruits and vegetables into bioactive and beneficial metabolites. This might alleviate the disease severity in patients with microbiota-associated diseases (Han and Xiao 2020).

Whole diets that have been shown to be beneficial for microbiota diversity are the Mediterranean and plant-based diets. Recent studies support the beneficial impact of a Mediterranean diet on microbiota profiles, as its consumption promotes greater microbial diversity, higher abundance of health-promoting bacterial taxa, and is associated with lower risk of depression (Jin et al. 2019; Berding et al. 2021; Kiani et al. 2022; Schneider et al. 2024). Plant-based diets are also related to differential microbial synthesis of metabolites, microbial richness and biodiversity of the gut microbiota (De Angelis et al. 2020). Although the vegan diet may be inadequate in calorific value, it is rich in dietary fibre, polyphenols, and antioxidant vitamins that boost the beneficial bacterial species. Vegan and vegetarian gut microbiota profiles both include a greater profusion of beneficial bacteria when compared to that of omnivores. On the contrary, the human gut microbiota appears to be altered with a greater impact in omnivores than in vegans, and is composed of bile-tolerant potentially harmful microorganisms (Berding et al. 2021). On the other hand, long-term consumption of a Western diet can lead to the extinction of beneficial microbes and decrease bacterial diversity (Berding et al. 2021; Malesza et al. 2021).

5.2. Psychobiotics beyond diet

While the effects of probiotics (i.e. living microorganisms) on gastrointestinal function are well-known, recent research has highlighted their broader influence on the body, including the CNS, and their potential benefit for patients with neurological, psychiatric and neurodegenerative disorders (Mörkl et al. 2020). Probiotics can interact with the gut microbiota at multiple levels, including the mucus layer, epithelial layer, and gut-associated lymphoid tissue (Sánchez et al. 2017). The probiotics can exert their benefits *via* competition with pathogens, improvement of the barrier function of the epithelial lining, immune-modulation, regulation of inflammation and immune responses, vagal neuro-transmission, and production of neuro-transmitters, such as GABA and serotonin, which play a role in brain function (Sánchez et al. 2017; Wieërs et al. 2019; Snigdha et al. 2022).

Fermented foods have been also shown to increase the diversity of gut microbiota and may have neuro-modulatory effects on cognition and mood (Schneider et al. 2024), which could be attributed to the production of metabolites that influence brain signalling (Schneider et al. 2024). Finally, prebiotics, containing no microorganisms, but only substances which stimulate their growth, can be obtained from various sources (breast milk, soybeans, raw oats, oligosaccharides contained in plants) (Oniszczuk et al. 2021) and might bolster the cognitive status, as well (Ni Lochlainn et al. 2024).

6. Future directions

Recent studies have substantially advanced our understanding of the gut microbiota and its connection to psychiatric, neurological, and neurodegenerative conditions. However, in order to apply this expanding knowledge to preventive measures and therapeutic procedures, further research and experiments are required. For example, deeper understanding about the impact of different diet patterns (e.g. periodic veganism patterns) on the gut microbial diversity, could reveal new ways of prevention based on diet improvement, especially in young children. Similarly, randomised studies may be required to understand the effects pre-, pro- and syn-biotics administration in adult or young patients with neurological disorders.

Moreover, the interplay between microbiotas from different parts of the human body demands further exploration. While much attention has been given to the gut microbiota, it is increasingly clear that microbiota from other organs, such as the lungs, also play critical roles in maintaining health and influencing disease. The dynamic interactions between these microbiota and how they communicate with the gut microbiota could offer valuable insights into previously unrecognised aspects of disease pathophysiology. Understanding these complex microbial ecosystems' interactions may lead to novel therapeutic strategies and open the door to personalised medicine, where treatments could be tailored to the individual's unique total-body microbiota profile.

Additionally, either stool- or serum-based metagenomics studies (metabarcoding) could provide valuable information for the identification of specific microbial taxes and metabolites and their link with each individual neuropsychiatric disease and disease severity. By correlating the concentration of different metabolites with established and routinely used psychiatric or mental health scales, we could develop new practical approaches to disease diagnosis and treatment. Prognostic algorithms based on microbiota

diversity and metabolite serum concentration could also help in personalised risk stratification and treatment intensification. To fully understand the complex role of the gut microbiota in neuropsychiatric disorders and develop effective medical interventions, interdisciplinary efforts are essential. Therefore, we believe that jointed multi-disciplinary efforts and consensus statements from neurologists, psychiatrists, and gastroenterologists are warranted to shed light on the gut-brain axis at the bedside (within a routine clinical setting) beyond the research bench.

7. Conclusions

Our review delves into the bidirectional communication between the gut and the brain, mediated by the microbiota-gut-brain axis. This complex interplay has profound implications for the pathophysiology of various disorders, such as schizophrenia, BD, MDD, ASD, ADHD, PD, AD, MS, migraine and epilepsy. We explore how specific dietary interventions and psychobiotics can modulate the gut microbiota, potentially leading to positive alterations in the brain function as well. Given the significantly reduced life expectancy of individuals with neuropsychiatric disorders, it is imperative to deepen our understanding of the pathways that constitute the gut-brain axis. By elucidating these mechanisms, we can pave the way for innovative therapeutic approaches and clinical applications that target the gut microbiota to improve the lives of those affected by these conditions.

Disclosure statement

No potential competing interest was reported by the authors.

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