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(Review Article)

Neurological disorders associated with impaired gut microbiota

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Abstract

A growing field of studies is focusing on the microbiota-gut-brain axis in order to better understand the bidirectional communication pathways between gut bacteria and the CNS. The pathophysiology of neurological disorders including Alzheimer's disease and autism has been attributed to dysregulation of gut-brain axis. Fecal microbiota transplantation is the method of transferring faeces from a healthy donor into the intestine of a recipient in order to restore the recipient's weakened intestinal flora. It's been used to treat a wide range of conditions, including recurrent *Clostridium difficile* infection and inflammatory bowel disease. Gut-brain psychology will aid studies on subjects such as character, memory and behaviour and will contribute to the advancement of general psychology as well as will add more light in the field of neuropsychology. *Lactobacillus* and *Bifidobacterium*, for example, are essential components of the gut microbiota. Oligosaccharides, unsaturated fatty acids, dietary fibers and polyphenols are the most popular prebiotics. Traditional fermented foods including yoghurt, natto and pickles help to balance the gut bacteria. The gut microbiota is shaped by a person's diet and gut-brain function is controlled by it. Different types of microbiota have different effects on the brain and actions through the microbiota–gut–brain axis. Via the microbiota-gut-brain axis, a healthy diet leads to a healthy gut microbiota and brain and mental health. Dysbiosis of the gut microbiota has been shown to trigger depression-like behaviours in GF mice. Proinflammatory mediators such as iNOS, ROS, COX_2 and NF-B are released by microglia, resulting in neuroinflammation in Alzheimer's disease. It is becoming more widely recognized as a symptom of Autism Spectrum Disorder. The establishment of gut-brain psychology is expected to have a significant impact on psychology and related disciplines.

Keywords: Gut-brain axis; Gut microbiota; Neurodegeneration; Probiotics; Neuroinflammation.

1 Introduction

The discovery that the gut microbiota (the trillions of microorganisms that live in the gut) and the microbiome (the genetic material of the microbiota) play a role in preserving homoeostasis and controlling almost every major body system, including the CNS, has ushered in a biomedical revolution over the last two decades. Animal studies also helped to demonstrate the importance of the microbiota in key aspects of neurodevelopment, neuroinflammation and behaviour. A new field of research known as the "microbiota-gut-brain axis" is being carried out to illuminate bidirectional messaging mechanisms in the GI tract and the central nervous system [1, 2]. Dysregulation of this axis has been linked to the pathophysiology of neurological conditions such as Alzheimer's disease [3], autism spectrum disorder [4, 5], Parkinson's disease [6, 7] and depression in the last 5 years [8,122]. We provide an update on the relationship between microbiota and brain function in the sense of neurological disorders in this Review.

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2 Pathways of gut brain axis

2.1 Neurology Pathway

The vagus nerve, the enteric nervous system and the function of neurotransmitters in the GI tract are all part of the neurologic pathway. GABA, serotonin, melatonin, histamine and acetylcholine are generated directly by neurologic modulation of afferent sensory nerves; this pathway also generates biologically active types of catecholamines in the gut lumen [11]. The autonomic nervous system also has an effect on gut immune system activation, for example, by directly modulating macrophage and mast cell responses to luminal bacteria. Furthermore, normal gut intrinsic primary afferent neuron excitability appears to be dependent on the gut microbiome [12,123].

2.1.1 Endocrine Pathway

The gut microbiota affects nutrient availability and, as a result, the release of biologically active peptides from enter endocrine cells, which may influence the gut-brain axis. The neuropeptide galanin, for example, is thought to play a role in a variety of important neurobiological functions, including nociception, sleep/wake cycle control, feeding, mood, blood pressure regulation, parental activity and neurotrophic functions. Galanin increases glucocorticoid secretion from the adrenal cortex by stimulating the central branch of the HPA axis (influencing the release of corticotrophin-releasing factor and adrenocorticotropic hormone) [13]. It may also directly induce cortisol secretion from the adrenal cortex as well as norepinephrine release from the adrenal medulla, indicating that it plays a role in the HPA axis response to stress [14,123].

2.1.2 Immune Pathway

During periods of dysbiosis, the gut microbiome influences inflammation metabolism in the GI tract, primarily through the immune system's release of cytokines such as interleukin [IL-10 and IL-4) and other cellular communication mediators, such as interferon-gamma. In Irritable Bowel Syndrome (IBS), irregular microbiota communities trigger mucosal innate immune responses, which increase gut epithelial permeability, activate gut pain sensory pathways and dysregulate the enteric nervous system [11, 15, 16]; both brain-gut and gut-brain dysfunctions occur, with the former being dominant [17]. Intestinal motility and secretion are affected by disruptions in the gut-brain axis, which contributes to visceral hypersensitivity and causes cellular changes in the enteroendocrine and immune systems [11,123].

2.2 Role of microbiota in Gut-Brain axis

More than 20 years ago, the first convincing evidence of a gastrointestinal microbe-brain interaction was discovered in humans [18]. Dysbiosis is often seen in Functional Gastrointestinal Disorders (FGID), which are due to a disturbance of GBA and are often associated with mood disorders [19-12, 125].

2.2.1 From gut microbiota to brain

In recent years, there has been a surge in experimental work, mostly on animals, aimed at determining the function of the microbiota in GBA modulation [20]. In both nervous systems, the absence of microbial colonization is linked to altered neurotransmitter expression and turnover [16]. After animal colonization in a bacterial species-specific fashion, all abnormalities are restored. GF (Germ-free) animals have lower anxiety and a higher stress response [24, 25; 17-28] with higher levels of ACTH and cortisol [17, 29]. In an age-dependent way [29], microbial colonization of the gut contributes to a normalization of the axis. Memory deficiency has been identified in GF animals [30], which has been linked to a change in the expression of Brain-Derived Neurotrophic Factor (BDNF). This molecule is involved in a variety of brain and cognitive functions, as well as muscle repair, regeneration and differentiation [31]. Research on the effect of gut microbiota manipulation by the use of probiotics and/or antibiotics have backed up the impact of microbiota on GBA [32]. Probiotics, on the other hand, decreased stress-induced cortisol release, as well as anxiety and depression-related activity [33]. A shift in the expression of subsets of genes involved in pain transmission and inflammation has also been identified in IBS (Irritable Bowel Syndrome), which was reset by the early life administration of antibiotics. The vagus nerve, which transmits information from the luminal environment to the brain, appears to be involved in microbiota contact with the brain [34]. Microbiota can interact with GBA in a variety of ways. The restoration of tight-junction integrity and the defense of the intestinal barrier are linked to probiotic species-specific central effects. The existence of neurotransmitter receptors on bacteria is needed for communication between the brain and the microbiota. Several studies have shown that bacteria have binding sites for enteric neurotransmitters provided by the host, which can affect the role of microbiota components. Pseudomonas fluorescence has been found to have a high affinity for the GABA mechanism, with binding properties similar to those of a brain receptor [35, 36,125].

2.2.2 From brain to gut microbiota

Just two hours of exposure to a social stressor will drastically alter the population profile and decrease the relative proportions of the major microbiota phyla [37]. It can also make you more susceptible to inflammation and infection triggers. Furthermore, the brain plays a key role in gut function modulation, including motility, acid, bicarbonate and mucus secretion, intestinal fluid handling and mucosal immune response. The disruption of the usual mucosal habitat caused by GBA dysregulation may then impact gut microbiota [38, 39]. Changes in intestinal permeability can also influence microbiota composition and work [40]. *Pseudomonas aeruginosa* expression is induced by norepinephrine released during surgery, which may lead to gut sepsis. Norepinephrine can also increase the virulent properties of *Campylobacter jejuni* and *Escherichia coli* by stimulating the proliferation of many strains of enteric pathogens. It's worth noting that stress-related changes in the gut promote the expression and spread of virulent bacteria. [41-44, 125].

2.3 Neurological disorders

2.3.1 Depression

The gut microbiota influences mood. In recent years, a growing number of studies have shown that the gut microbiota of patients with Major Depressive Disorder (MDD) differs from that of healthy controls. When compared to safe controls, MDD patients had more Actinobacteria and less Bacteroidetes, according to Zheng et al. [45], in contrast to safe controls, MDD patients had significantly higher Bacteroidetes, Proteobacteria and Actinobacteria, but significantly lower Firmicutes, according to Jiang et al. [46], Lin et al. [36] also discovered that MDD patients had more Firmicutes and fewer Bacteroidetes at the phylum level than safe controls. Despite the fact that the findings were not identical, they both agreed that the gut microbiome of MDD patients had changed. Interestingly, dysbiosis of the gut microbiota has been shown to trigger depression-like behaviours in GF mice in some studies. For example, Zheng et al. [45] found that GF mice colonized with MDD patients faecal microbiota showed depression-like behaviours and host metabolism disruptions as compared to colonization with healthy controls' microbiota. Kelly et al. [48] confirmed that transplanting GF mice with faecal microbiota from depressed patients could cause depression-related behaviours, which is in line with Zheng's hypothesis [119]. These findings indicate that dysbiosis of the gut microbiota is a contributing factor in MDD. Furthermore, dysbiosis of the gut microbiota has been linked to MDD in some studies. According to Jiang et al. [46], MDD patients had higher levels of *Enterobacteriaceae* and *Alistipes*, but lower levels of *Faecalibacterium*, which was negatively associated with depression severity. MDD patients had lower levels of *Bifidobacterium* and *Lactobacillus* than safe controls, according to Aizawa et al. [39], which may be linked to the production of MDD. MDD patients had more *Prevotella, Klebsiella, Streptococcus* and *Clostridium* XI at the genus level, according to Lin et al. [36]. Furthermore, during the diagnosis of MDD patients, Prevotella and Klebsiella levels were consistent with the Hamilton depression rating scale. Kelly et al. [48] also found that when depressed patients were compared to healthy controls, *Prevotellaceae* was lower but *Thermoanaerobacteriaceae* was higher. In depressed rats, Yu et al. [37] discovered that gut microbiota dysbiosis is significantly linked to altered tryptophan and bile acid metabolism. Probiotics including *Lactobacillus rhamnosus* [49], *Lactobacillus helveticus* [27], *Bifidobacterium longum* [64] and *Bifidobacterium infantis* [50], as well as prebiotics including FOS+GOS, have been shown to reduce depression-related actions [51]. Furthermore, probiotic therapy in humans has been shown to minimize self-reported depression, increase self-reported satisfaction and reduce ruminative thought [52].

2.3.2 Alzheimer's disease

Alzheimer's Disease (AD) is the most common type of dementia in the elderly. It is a progressive and permanent neurodegenerative disease. Patients with Alzheimer's disease have severe CNS dysfunctions in learning, memory and behavioural problems, resulting in everyday activity impairment [53, 54]. Alzheimer's disease (AD) is characterized by the loss of neurons and progressive synaptic dysfunction, as well as the deposition of Amyloid-β (Aβ) peptide outside or around neurons and the accumulation of hyperphosphorylated protein tau within cortical neurons [55–57]. Microtubule destabilization, synaptic deficiency, disturbance of Ca^{2+} homeostasis in neurons and eventually neuronal apoptosis are all caused by Aβ overload and tau aggregation [58, 59]. Despite recent scientific developments, the mechanisms underlying AD remain unknown and existing Aβ-targeted therapies only provide minor symptom relief [60]. Previous research has suggested that the pathogenesis of Alzheimer's disease is linked to peripheral infectious origins, which may induce CNS neuroinflammation [61, 62]. In mice, Herpes Simplex Virus type 1 (HSV_1) infection is closely related to Aβ and tau deposition in Alzheimer's disease. The expression of the gene encoding Cholesterol 25-Hydroxylase ($CH_{25}H$), which is essential for modulating both AD susceptibility and Aβ output, is selectively upregulated by virus infection [63, 64]. In addition, previous research has found possible mechanistic links between AD pathology and other infections including *spirochete*, *fungus* and *Chlamydia pneumoniae* infections [65–66]. Similarly, recent research has linked the gut microbiome to the aetiology of Alzheimer's disease. The presence of a metabolic enzyme from the microbiota in the cerebrospinal fluid of Alzheimer's disease patients, which is linked to biomarkers of the disease (phosphorylated tau and phosphorylated tau/A42), suggests that the gut microbiota is involved in the pathogenesis of the disease [67]. When compared to APP mice in control conditions, APP-mutant germ-free mice have less cerebral Aβ amyloid pathology in an Aβ Precursor Protein (APP) transgenic mouse model. Reconstructing these germ-free APP mice with microbiota from traditional mice [68] could block anti-Aβ results. In addition, long-term broad-spectrum antibiotic therapy decreases Aβ deposition and enhances the neuropathological phenotype of mice with Alzheimer's disease [69]. When comparing the faecal microbiomes and faecal SCFAs of AD mice and WT mice at various ages, dramatic increases in *Verrucomicrobia* and *Proteobacteria*, as well as significant reductions in *Ruminococcus* and *Butyricicoccus*, are observed in AD mice, implying altered microbiota composition and diversity, while the lower level of SCFAs indicates alterations in several metabolites. Activated microglia have also been shown to lead to the pathology of Alzheimer's disease by inhibiting Aβ clearance and enhancing Aβ deposition in previous studies [70]. Increased Aβ deposition causes the release of Proinflammatory mediators such as iNOS, ROS, COX_2 and NF-B by microglia, resulting in neuroinflammation in AD pathogenesis [70]. These findings suggest that various species of gut microbiota cause a signalling pathways and contribute to the pathogenesis of Alzheimer's disease. Nutritional interventions or probiotics/antibiotics can become novel therapeutic strategies to slow the progression of Alzheimer's disease as more microbial taxa are studied [124].

2.3.3 Parkinson's disease

Parkinson's disease is a neurological disorder that affects people. While motor symptoms remain the clinical hallmarks of Parkinson's disease, gastrointestinal symptoms (along with other non-motor symptoms) are present and have a greater impact on patient quality of life. Problems with the autonomic and enteric nervous systems, such as slow-transit constipation and sensory alterations, are among the non-motor symptoms. With infrequent bowel movements and the intensity of constipation, the likelihood of Parkinson's disease rises and there is a significant comorbidity of Parkinson's disease and IBS-like symptoms. Furthermore, constipation is one of the earliest symptoms, occurring 15.3 years before motor dysfunction. Clinical studies of Parkinson's disease and the gut microbiota have so far been restricted to comparing assemblage variations to healthy controls and some of the recorded differences may be due to slowed colonic transit [121]. However, recent research indicating that microbiota from Parkinson's patients, but not healthy controls, improves physical impairments in a Parkinson's rat model indicates causation [71]. As a result, prodromal gastrointestinal symptoms may exist, making the gut microbiota a promising source of knowledge for diagnosis, prognosis and, theoretically, pathogenesis.

2.3.4 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a group of disorders GI symptoms are general and contribute significantly to the morbidity of ASD patients, in addition to the core symptoms (difficulty with social and communicative actions, repetitive behaviours). In preclinical models, GI symptom intensity is closely linked to ASD symptom severity, as well as anxiety and sensory over-responsivity conditions modulated by gut microbiota. Gut dysbiosis is becoming more widely recognized as a symptom of ASD, however, as with other clinical conditions, causality is still based on interesting, but untested theories and findings from unregulated clinical trials [72]. In conclusion, there is growing evidence that the gut microbiome is involved not only in the normal development and function of the nervous system, but also in a variety of acute and chronic diseases that affect the gut and nervous system throughout life. It's unclear if the gut microbiota is causal, but its facilitation of pathogenesis and potentiation of severity in disease models indicates it's not only a side effect of the underlying aetiology. Given the substantial preclinical evidence for both top-down and bottom-up approaches.

2.4 Promoting mental and brain health by targeting the microbiota–gut–brain axis

The establishment of gut-brain psychology is expected to have a significant impact on psychology and related disciplines. Gut-brain psychology will aid studies on subjects such as character, memory and behaviour and will contribute to the advancement of general psychology. It can also shed light on contentious issues, such as the study of unconsciousness. However, therapeutic applications, such as controlling the brain and actions by gut microbiota interference, are likely to have a greater impact [120]. The related studies and applications would undoubtedly have a broad influence on a variety of fields, including psychology, medicine, food and the environment [73]. The GF technique, pathogen infection, antibiotics, FMT, probiotics, prebiotics and diet are the main microbiota interventions [74 -77]; all of the methods have shown great potential in regulating mind and behaviour [74, 75, 1, 91, 77-79]. The first two approaches are only feasible in laboratory animals, the third is typically used in anti-infection and the last four are all promising in improving microbiota. Fecal microbiota transplantation is the method of transferring faeces from a healthy donor into the intestine of a recipient in order to restore the recipient's weakened intestinal flora. It has been successfully used to treat a variety of diseases, including recurrent *Clostridium difficile* infection and inflammatory bowel disease and its enhanced model-selective microbiota transplantation-has also been used [75, 81]. FMT remoulds the intestinal microbiota, which enhances not only digestive function but also brain and actions [78]. According to recent studies, FMT can be used to treat a variety of brain disorders, including ASD [83], Tourette syndrome [84] and epilepsy [85]. *Lactobacillus* and *Bifidobacterium,* for example, are essential components of the gut microbiota and their derivatives are commonly used in modern medications [86-89]. To highlight the potential of certain probiotics in mental illness treatment, Dinan et al. (2013) coined the term "psychobiotics." Psychobiotics with good antidepressant, anti-anxiety and/or anti-autism effects have been identified in animal and clinical studies [88-90]. These psychobiotics are more likely to function by improving the microbiota–gut–brain axis and regulating gut microbiota [91, 92, 94- 97]. Oligosaccharides, unsaturated fatty acids, dietary fibres and polyphenols are the most popular prebiotics [77, 98, 99]. Prebiotics, such as omega-3 fatty acids and oligosaccharides, have been shown in studies to alter the gut microbiota, enhancing the microbiota–gut–brain axis role and symptoms in mental illness patients [77, 100 -103]. A diet high in dietary fibres strengthens the intestinal barrier, increases gut microbiota diversity, controls glycol-metabolism by enhancing glucose regulation and insulin sensitivity, modulates lipid metabolism by lowering low-density lipoprotein and cholesterol content and promotes gut-brain health [104 -108] . Traditional fermented foods including yoghurt, natto and pickles help to balance the gut microbiota and support gut-brain health. Diets high in fermented foods, dietary fibres and unsaturated fatty acids, such as the Mediterranean and Japanese diets, promote the growth of beneficial microorganisms and enhance health and wellbeing [109 -111]. Healthy diets, such as high-fat, high-reined carbohydrate and low-MACs diets, are thought to encourage the role of the microbiota–gut–brain axis and contribute to changes in health and well-being, whereas unhealthy diets, such as high-fat, high-reined carbohydrate and low-MACs diets, are thought to damage mood and memory [112-116, 111]. Allen et al. (2017) suggested nutritional psychology as a means of linking the microbiota–gut–brain axis to psychology. Nutritional psychology, in our view, asserts that the gut microbiota is intimately linked to the mind and behaviour [117]. The most influential factor for the gut microbiota is food, which has an impact that lasts a lifetime. The gut microbiota is shaped by a person's diet and gut-brain function is controlled by it. Different types of microbiota have different effects on the brain and actions through the microbiota–gut–brain axis. Via the microbiota–gut–brain axis, a healthy diet leads to a healthy gut microbiota and gut-brain and promotes brain and mental health. Meanwhile, a poor diet disrupts the gastrointestinal microbiota and impairs gut-brain balance, causing microbiota–gut–brain axis dysfunction and ultimately harming the brain and wellbeing. Dietotherapy is the practise of modifying one's diet to improve one's health. It's been used as an adjuvant treatment for mental illness recovery for a long time, but its mechanisms are also questioned [118-120]. Traditionally, research has concentrated on the role of specific foods or substances.

3 Discussion and conclusion

The bidirectional communication pathways between gut bacteria and the CNS which is more popular now a days as “microbiota-gut-brain axis” is the subject of a growing body of research. Dysregulation of this axis has been linked to the pathophysiology of neurological conditions such as depression, Alzheimer's disease, autism spectrum disorder, multiple sclerosis and Parkinson's disease. The neuropeptide galanin is thought to play a role in a variety of important neurobiological functions, including nociception, sleep/wake cycle control, feeding, mood, blood pressure regulation, parental activity and neurotrophic functions. The gut microbiota of patients with major depressive disorder (MDD) differs from that of healthy controls. When compared to safe controls, MDD patients had more Actinobacteria and less Bacteroidetes. Dysbiosis of the gut microbiota has been shown to trigger depression-like behaviours in GF mice in some studies. In depressed rats, gut microbiota dysbiosis is significantly linked to altered tryptophan and bile acid metabolism. These findings indicate that dysbiotic gut microbiota is a contributing factor in MDD and may be linked to the production of MDD. Alzheimer's disease is the most common type of dementia in the elderly. It is a progressive and permanent neurodegenerative disease with learning, memory and behavioural problems. Previous research has suggested that the pathogenesis of Alzheimer's is linked to infectious origins. In mice, herpes simplex virus type 1 (HSV1) infection is closely related to Aβ and tau deposition in Alzheimer's disease. When compared to APP mice in control conditions, APP-mutant germ-free mice have less cerebral Aβ amyloid pathology in an Aβ precursor protein (APP) transgenic mouse model. Reconstructing these mice with microbiota from traditional mice could block anti- Aβ results. In addition, long-term broad-spectrum antibiotic therapy decreases Aβ deposition and enhances the neuropathological phenotype of mice with AD. Proinflammatory mediators such as iNOS, ROS, COX_2 and NF-B are released by microglia, resulting in neuroinflammation in AD pathogenesis. These findings suggest that various species of gut microbiota cause a signaling pathways and contribute to the pathogenesis of Alzheimer's disease. Gut dysbiosis is becoming more widely recognized as a symptom of Autism Spectrum Disorder. It's unclear if the gut microbiota is causal, but its facilitation of pathogenesis and potentiation of severity in disease models indicates it's not only a side effect of the underlying aetiology. Establishment of gut-brain psychology is expected to have a significant impact on psychology and related disciplines. The GF technique, pathogen infection, antibiotics, FMT, probiotics, prebiotics and diet are the main microbiota interventions. Fecal microbiota transplantation is the method of transferring faeces from a healthy donor into the intestine of a recipient in order to restore the recipient's weakened intestinal flora. According to recent studies, it can be used to treat a variety of brain disorders, including ASD and Tourette syndrome. Psychobiotics with good antidepressant, anti-anxiety and/or anti-autism effects have been identified in animal and clinical studies. These psychobiotics are more likely to function by improving the microbiota-gut-brain axis and regulating gut microbiota. Prebiotics, such as omega-3 fatty acids and oligosaccharides, have been shown in studies to alter the gut microbiota. Diets high in dietary fibers promote the growth of beneficial microorganisms and enhance health. Traditional fermented foods including yoghurt, natto and pickles help to balance gut microbiota and support gut-brain health. Healthy diets encourage the role of the microbiota-gut-brain axis and contribute to well-being. A poor diet disrupts the gastrointestinal microbiota and impairs gut-brain balance. This, in turn, can harm the brain and mental health of people with mental illness.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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