The Gut–Brain Axis within the Human Body

Subjects: Microbiology

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The human gut microbiota (GM) is a complex microbial ecosystem that colonises the gastrointestinal tract (GIT) and is comprised of bacteria, viruses, fungi, and protozoa. The GM has a symbiotic relationship with its host that is fundamental for body homeostasis. The GM is not limited to the scope of the GIT, but there are bidirectional interactions between the GM and other organs, highlighting the concept of the “gut–organ axis”. Any deviation from the normal composition of the GM, termed ”microbial dysbiosis”, is implicated in the pathogenesis of various diseases. Only a few studies have demonstrated a relationship between GM modifications and disease phenotypes, and it is still unknown whether an altered GM contributes to a disease or simply reflects its status. Restoration of the GM with probiotics and prebiotics has been postulated, but evidence for the effects of prebiotics is limited. Prebiotics are substrates that are “selectively utilized by host microorganisms, conferring a health benefit”.

gut–organ axis gut microbiota dysbiosis prebiotics

1. Introduction

The significance of the GM to human health has been recognised for centuries; Hippocrates said, “Death sits in the bowls” in 400 B.C., and the term “microbiota” dates back to the early 1900s [1]. The human GM is the largest micro-ecosystem in the human body and is regarded as the “essential organ” [2]. The GM is a complex, dynamic, and spatially heterogeneous ecosystem comprised of a collection of bacteria, viruses, fungi, and protozoa that colonise the gastrointestinal tract (GIT) and interact with each other and the human host [3]. The human body harbours a nearly equal quantity of microbial cells, in comparison to human cells [4]. The regions with the highest microbial biomass are the caecum and proximal colon.

The GM profile of each individual is unique at the species and genus level and is influenced by several factors, such as genetics, diet, environmental conditions, lifestyle, early microbial exposure, and the immune system [5]. However, the relative abundance and distribution at the phylum level along the intestine are consistent among healthy individuals [6]. The gut of an adult individual is majorly dominated by six phyla, including *Firmicutes* (*Clostridium*, *Lactobacillus*, and *Enterococcus*), *Bacteroidetes* (*Bacteroides*), *Actinobacteria* (*Bifidobacterium*), *Proteobacteria* (*E. coli*), *Fusobacteria*, *Verrucomicrobia*, and *Cyanobacteria*, among which *Firmicutes* and *Bacteroidetes* are the major types [7]. Also, fungi, mainly *Candida*, *Saccharomyces*, *Malassezia*, and *Cladosporium*, are included in the GM, as are viruses, phages, and archaea, mainly *Methanobrevibacter smithii* [8][9].

The GM has a symbiotic relationship with the host, while it has a central role in maintaining the homeostasis of the human body, impacting various physiological functions, including metabolism, vitamin synthesis, barrier homeostasis, protection against pathogens, immune system development and maturation, and hematopoiesis via intestinal and extra-intestinal actions, having an effect on human behaviour and thereby making it a vital organ [3] [10]. The influence of the GM is not limited to the scope of the GIT, but evidence from recent studies describes bidirectional interactions between the GM and other organs, highlighting the concept of the "gut–organ axis" (**Figure 1**). This cross-talk is mediated by a variety of signalling pathways and direct chemical interactions between the host and microorganisms [10]. Studies over the past five years have increased the understanding of the gut–brain axis, the gut–liver axis, the gut–lung axis, and the gut–heart axis [11].

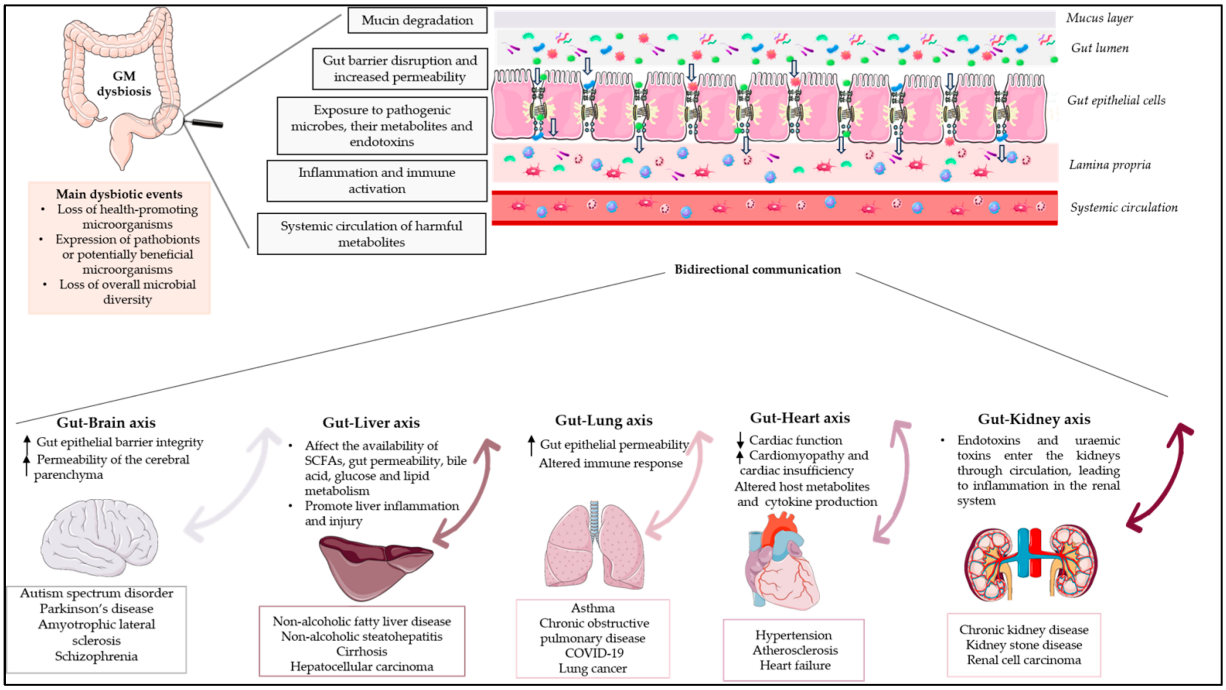

Figure 1. Schematic diagram depicting the influence of GM dysbiosis on the gut–organ axis. GM dysbiosis leads to the degradation of mucin, disrupts the gut's protective barrier, increases its permeability, and enables pathogenic microorganisms, along with their by-products and endotoxins, to infiltrate. This invasion results in the activation of immune cells and triggers systemic inflammation through the peripheral circulation. The impact of GM dysbiosis extends beyond the gastrointestinal tract. Recent research indicates two-way interactions between the GM and various organs, emphasizing the idea of a "gut–organ axis". This communication is facilitated through a range of signalling pathways and direct interactions between the host and the GM. Arrows indicate a bidirectional relationship between the gut and each organ. Parts of the figure were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/ accessed on 25 August 2023).

Any deviation from the normal composition of the GM, termed "microbial dysbiosis", is characterised by an imbalance in the composition and/or function of the microbial ecology. Dysbiosis has been classified into numerous types or combinations of types, including (1) the loss of health-promoting microorganisms; (2) the expression of

pathobionts or potentially beneficial microorganisms; and (3) the loss of overall microbial diversity (**Figure 1**) [12]. Environmental factors as well as host-related factors can influence homeostasis, such as perinatal disruption of colonization, genetics, diet, disease, and stress [13]. Several studies have highlighted the dysbiosis of the GM during the course of diseases such as inflammatory bowel disease (IBD), malnutrition, metabolic disorders, asthma, and neurodegenerative diseases. In most diseases, it has been reported that altered microbiota causes pathophysiologies in vital human organs; however, few studies have demonstrated the causal relationship between microbial alterations and disease phenotypes, and it remains unclear whether the altered GM contributes to a disease or simply reflects its status [13].

According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are substrates that are “selectively utilized by host microorganisms, conferring a health benefit” [14]. Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), lactulose, and inulin are the most widely recognised prebiotics, whereas β-glucans derived from various mushroom species (e.g., *Pleurotus eryngii*) are potential prebiotic candidates [15]. Recently, whole-food-based treatments have been used to modulate the GM through potential synergistic interactions between food’s various components [15]. Restoration of the GM in various diseases with pro/prebiotics has been postulated, but evidence for the effects of prebiotics is scarce.

2. The Gut–Brain Axis

The gut–brain axis comprises a complex physiological system that enables bidirectional communication between the gut and the host nervous system. [16]. This bidirectional communication within the gut–brain axis elucidates how messages from the GM influence brain function and how signals from the brain impact gastrointestinal physiology and gut microbial activity [17]. These bidirectional communications involve the central nervous system (CNS), intrinsic branches of the enteric nervous system (ENS), extrinsic parasympathetic and sympathetic branches of the autonomic nervous system (ANS), the hypothalamic–pituitary–adrenal axis (HPA), neuroimmune pathways (neurotransmitters, hormones, and neuropeptides), and the gut microenvironment [15][18]. The HPA axis, a component of the limbic system, is considered the central stress efferent axis that coordinates the organism’s adaptive responses to all stressors. Environmental stress and elevated systemic pro-inflammatory cytokines activate this system, which, via the secretion of the corticotropin-releasing factor from the hypothalamus, stimulates adrenocorticotropic hormone secretion from the pituitary gland, which ultimately results in cortisol release from the adrenal glands [6]. Thus, the combination of neural and hormonal lines of communication allows the brain to influence the activities of gut functional effector cells, including immune cells, epithelial cells, and enteric neurons [19]. On the other hand, these same cells are influenced by the GM, which may influence these central processes directly and indirectly via immune system activation, the production of neurotransmitters, and the production of short-chain fatty acids (SCFAs) and key dietary amino acids such as tryptophan and its metabolites [20]. Furthermore, the GM can act through the permeability of the gut barrier, with an increase in circulating lipopolysaccharide (LPS), modulating the levels of brain-derived neurotrophic factor and altering neuroendocrine and neural pathways.

In addition, the brain affects gut peristalsis, and sensory and secretion function, mainly via the vagus nerve. The vagus nerve, which transmits information from the luminal environment to the CNS, is the major nerve of the parasympathetic system of the ANS and a crucial modulatory constitutive direct communication pathway between the GM and the brain [21]. The vagus nerve consists of sensory and motor neurons and has been extensively studied for its involvement in hunger, satiety, and stress response but also for its major role in the regulation of inflammation via neuronal motor efferents [22].

The gut–brain axis is expected to have many effects on mood, motivation, and higher cognitive functions, in addition to ensuring that gastrointestinal homeostasis is properly maintained [6]. Disruption of the delicate balance between host and gut bacteria could be a contributing factor behind various diseases. The dysregulation of the gut–brain axis has been linked by numerous researchers to various immunologic, neurologic, and psychiatric disorders.

2.1. Gut Dysbiosis in Neurologic Diseases

GM dysbiosis interferes with the development of local and systemic inflammatory states, resulting in altered gut epithelial barrier integrity, allowing the release of hormones, microbial metabolites, and components by the GM that reach the brain via the vagus nerve, crossing the blood–brain barrier, and inducing neurodegenerative processes [23]. Moreover, dysbiosis increases the permeability of the cerebral parenchyma, which may result in neuroinflammation and dysfunctional neuronal cells. Emerging research indicates that gut dysbiosis may influence the onset and progression of a variety of neurological disorders, such as autism spectrum disorder (ASD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and schizophrenia. **Table 1** provides a summary of the main dysbiotic events on the GM composition identified in neurological disorders. Subsequent sections will delve into the analysis of representative diseases and their associated dysbiotic events.

2.1.1. Dysbiosis in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a complex group of neurodevelopmental disorders characterised by aberrant social interactions and communication, repetitive and stereotyped patterns of behaviour, and abnormal sensory responses. [24]. According to a recent systematic literature review, the prevalence of ASD in US children ranked 1.70 and 1.85% in children aged 4 and 8 years, respectively, while the prevalence in Europe ranged between 0.38 and 1.55% [25]. Although genetic and environmental factors have been linked to the development of ASD, the precise etiology remains unknown. Recent research has highlighted the role of the gut–brain axis in various neuropsychiatric disorders, including autism spectrum disorder. In addition, individuals with ASD frequently experience gastrointestinal disturbances, such as constipation, diarrhoea, flatulence, increased gut permeability, and abdominal pain [26][27].

Several studies have highlighted differences in the GM composition between ASD and neurotypical children [28]. It should be noted, however, that among studies related to ASD, no specific microbial species has been found to be significantly different, as various factors such as diet, age, sex, population, and severity of autism should be taken into account [28]. Although changes in the GM composition of autistic children are not always consistent across

studies, patients frequently exhibit microbial imbalances of multiple types, including higher abundances of *Bacteroides*, *Parabacteroides*, *Clostridium*, *Faecalibacterium*, and *Phascolarctobacterium* and a lower relative abundance of *Streptococcus* and *Bifidobacterium* [26][29].

The gastrointestinal symptoms of individuals with ASD seem to be significantly correlated with the degree of behavioural and cognitive impairment. For example, in individuals with ASD, irritability, aggressiveness, sleep disturbances, and self-injury are strongly associated with GI symptoms [26][30]. This evidence suggests that gastrointestinal abnormalities, perhaps linked to gut dysbiosis, may be associated with ASD [31]. Consistent with this hypothesis, a meta-analysis by Iglesias-Vázquez et al. [29] suggests that there is a dysbiosis in ASD children that may influence the development and severity of ASD symptomatology. More specifically, this study concluded that the microbiota of ASD individuals was mainly composed of the phyla Bacteroidetes, Firmicutes, and Actinobacteria and also showed a significantly higher abundance of the genera *Bacteroides*, *Parabacteroides*, *Clostridium*, *Faecalibacterium*, and *Phascolarctobacterium* and a lower percentage of *Coprococcus* and *Bifidobacterium*. Taken together, all these alterations in the GM could be associated with increased GI disturbances in individuals with ASD.

2.1.2. Dysbiosis in Parkinson's Disease

Parkinson's disease (PD) is the second most common degenerative disorder of the brain, affecting seven to ten million people worldwide [32]. PD is mainly characterised by multifactorial motor and non-motor symptoms, including resting tremor, muscular rigidity, slowness of movement, and gait abnormality, as well as cognitive disturbances, depression, mood deflection, sensory alternations, and sleep alternations [32][33]. The principal pathology of PD is characterised by the loss of dopamine-producing neurons present in a specific region of the brain, known as the substantia nigra, accompanied by the accumulation of alfa-synuclein (alfa-syn) in the form of Lewy bodies and Lewy neurites, a condition known as synucleinopathy [34].

Complex genetic and environmental factors are involved in the etiology of PD; however, the cause of PD remains unknown. Gastrointestinal symptoms are observed in most PD patients, including hypersalivation, dysphagia, constipation, nausea, altered bowel habits, and defecatory dysfunction [32]. Several studies have demonstrated GM abnormalities in patients with PD [35][36][37]. A meta-analysis conducted by Romano et al. [38] re-analysing the ten currently available 16S microbiome datasets found significant alterations in the PD-associated microbiome. More specifically, the authors concluded that enrichment of the genera *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* and depletion of bacteria belonging to the *Lachnospiraceae* family and the *Faecalibacterium* genus, emerged as the most consistent PD gut microbiome changes, suggesting that the observed dysbiosis may be a result of pro-inflammation, which could be linked to the GI symptom manifestation in PD patients [38]. In another study, consistent increases were principally shown in the family *Verrucomicrobiaceae*, genus *Akkermansia*, and species *Akkermansia muciniphila*, while health-promoting genera and butyrate producers *Roseburia* and *Faecalibaterium* were reported to decrease in PD patients [39]. Emerging studies have shown the correlations between GM alterations and the phenotypes of PD, including both motor and non-motor symptoms [40][41][42]. These alterations in the GM of patients may reveal a mechanism, as this observed dysbiosis has been associated with increased

intestinal barrier permeability and subsequent gut inflammation. This hypothesis is supported by a number of studies that demonstrate that GM dysbiosis in PD is shown to be associated with the disrupted intestinal barrier, which is closely associated with gut inflammation, an established symptom in PD patients [43][44].

2.1.3. Dysbiosis in Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease defined by progressive loss of cortical, brain stem, and spinal motor neurons, resulting in weakness and wasting of the musculature [45][46]. In addition, ALS presents extra-motor features, including cognitive and behavioural disturbances [47]. Over 90% of ALS cases are sporadic (sALS) and of unknown cause, while the remaining 10% are familial (fALS) since they carry a mutation in one of the disease-related genes [47]. Mutations of superoxide dismutase 1 (SOD1), FUS RNA binding protein (FUS/TLS), C9orf72-SMCR8 complex subunit (C9orf72), and TAR DNA binding protein (TARDBP/TDP-43) are more commonly associated with ALS [48].

ALS etiology and pathophysiology require further elucidation, and in spite of massive efforts having been invested, there is no cure available at present, leading to death by respiratory failure within 2–5 years from symptom onset [49]. Recent studies demonstrate a strong pathophysiological crosstalk between the GM and ALS [50]. ALS pathogenesis has been linked to alterations in GM composition, impaired metabolism, an altered innate immune response, and the production of gut-derived neurotoxins by Clostridia species that induce brain damage [50].

Due to a number of factors, such as the small sample size, the observed heterogeneity within the study population, the various experimental procedures and data analysis, and the heterogeneity of the GM regardless of health status, the results of human studies conducted to determine the potential role of the GM in ALS patients are frequently inconclusive. Despite the contradictory results among the studies, some important findings could be observed, which include the following: (1) Differences in the GM populations between ALS patients and healthy individuals. For example, in the study of Fang et al. [51], which examined six ALS patients and five healthy people without ALS, the authors demonstrated significant differences in GM composition between the two groups. More specifically, in the gut of ALS patients, a reduced ratio of Firmicutes/Bacteroidetes was accompanied by a decreased abundance of butyrate-producing *Oscillibacter*, *Anaerostipes*, and *Lachnospira* counts and an increased abundance of glucose-metabolizing Dorea. More recently, comparing the GM of 10 ALS patients and their spouses (n = 10), it was found that the populations of the ALS patients' GM were more diverse and deficient in *Prevotella* spp., suggesting that modifying the gut microbiome, such as via amelioration of *Prevotella* spp. deficiency, and/or altering butyrate metabolism, may have translational value for ALS treatment [52]. (2) GM composition alters during the course of the ALS. Gioia and colleagues [53] studied the GM of 50 ALS patients and 50 matched controls and demonstrated that the GM of ALS patients differed from that of controls. Also, the composition of the intestinal microbiota changed as the disease progressed, as indicated by a significant decrease in the number of operational taxonomy units observed during the follow-up. Intriguingly, an imbalance between potentially protective microbial groups, such as Bacteroidetes, and those with potential neurotoxic or pro-inflammatory activity, such as Cyanobacteria, has been observed.

Overall, these findings indicate the implication of the GM in ALS disease; however, it has been difficult to ascertain whether these changes in the GM are the cause of ALS, an aggravating factor for the disease, or the result of the disease. Additional human clinical research evidence is required in order to establish the exact role of the GM in the pathogenesis of ALS.

2.1.4. Dysbiosis in Schizophrenia

Schizophrenia is a complex, heterogeneous, neurodevelopmental disorder with deficits across many dimensions [54]. The expression of the underlying genetic vulnerability is shaped by a multifaceted combination of prenatal and early postnatal environmental factors [55][56]. These factors may sensitise a developing brain and its information processing ability to the subsequent accumulation of additional environmental insults, which may overwhelm compensatory capacities during adolescence and emerge as psychotic symptoms [57]. Subtle deficits in cognition, social communication, and functioning are often evident prior to the onset of overt psychotic symptoms [58], and the majority of people experience recurring psychotic relapses with variable degrees of functional impairment [59].

A precise integrative mechanistic understanding of the interaction of genetic and environmental processes across the neurodevelopmental trajectory in this condition remains elusive. The link between schizophrenia and the GM has garnered increasing attention in recent years. The main findings of existing studies examining the link between the GM and schizophrenia include the following:

(a) Patients with schizophrenia have a deviant GM compared to healthy controls. The diversity and composition of the GM were substantially altered in schizophrenia patients, according to these findings [60][61]. Zheng et al. [60] found significant alterations in beta diversity but not alpha diversity between the GM of patients and controls. In the schizophrenia group, an enhanced count of bacterial families like *Prevotellaceae*, *Veillonellaceae*, *Bacteroidaceae*, and *Coriobacteriaceae* was observed compared to healthy controls, while *Ruminococcus* and *Roseburia* abundances were significantly lower in patients with schizophrenia.

(b) Specific bacteria may function as biomarkers to differentiate patients with schizophrenia from healthy individuals [62][63]. Shen et al. identified 12 biomarkers that could be used as diagnostic factors to differentiate the schizophrenia cohort from the control cohort, including *Gammaproteobacteria* (at class level), *Enterobacteriales* (at order level), *Alcaligenaceae*, *Enterobacteriaceae*, and *Lachnospiraceae* (at family level), *Acidaminococcus*, *Phascolarctobacterium*, *Blautia*, *Desulfovibrio*, and *Megasphaera* (at genus level), and *Plebeius fragilis* (at species level).

(c) Differences in the GM between remission and acute schizophrenia. Pan et al. [63] demonstrated differences between acute and remission patients, indicating that alterations in the intestinal microbiota may influence the prognosis of the disease and suggesting the GM's potential as a non-invasive diagnostic tool.

(d) Differences in the GM between first-episode drug-naïve and chronically medicated schizophrenia patients [64]. Chronically antipsychotic-treated schizophrenia patients showed lower microbial richness and diversity as compared to first-episode drug-naïve schizophrenia patients and healthy controls, suggesting that the gut

microbiome may be implicated in the pathophysiology of schizophrenia via modulation of specific brain structures [64].

(e) The role of the gut–brain axis. The GM was found to be associated with schizophrenia via processes involved in the gut–brain axis, including immune-regulating pathways, neurotransmitter synthesis, the production of bioactive microbial metabolites, and tryptophan metabolism [65]. Schizophrenia-related behaviour has been observed in mice by Zheng et al. [60], who demonstrated that transplantation of the GM from schizophrenia patients induces schizophrenia-like behaviours in germ-free recipient rodents, suggesting that the GM can affect the brain neurochemistry associated with the onset of schizophrenia.

2.2. The Role of Prebiotics in Neurological Diseases

In recent years, different studies, including mostly in vitro and in vivo studies, and only a few human studies, have shown the beneficial effects of prebiotics on brain function [66][67]. The proposed mechanisms for prebiotic-based modulation of the GM–brain axis include the following [68][69][70]: (i) decreased inflammation in gut inflammatory disorders, preventing the presence of inflammatory compounds in the brain; (ii) improvement of GM composition and modulation of brain function, enhancing the composition of the GM; and (iii) influence on the production of neurochemicals. In addition, it has been suggested that, compared to probiotics, prebiotics could be advantageous due to probiotics' inability to survive in the GI tract [68].

Numerous clinical studies examine the impact of probiotics and symbiotics on neurological conditions [71][72][73]. On the other hand, the supplementation of prebiotics to manipulate the GM as a novel treatment for neurological diseases has not been investigated, and there are only a few human studies that examine the effectiveness of prebiotics, while in ALS there have been no clinical studies (**Table 2**). The first study to examine the effects of prebiotics on ASD was conducted by Grimaldi et al. [74]. More particularly, the authors assessed the impact of a prebiotic (B-GOS® mixture, Clasado Biosciences Ltd., Reading, UK) on GM composition and metabolic activity in 30 autistic children. According to the results, the administration of B-GOS led to modulation of the GM composition in autistic children following unrestricted diets. This modulation primarily affected bifidobacterial populations and also affected other bacterial groups, including members of the *Lachnospiraceae* family such as *Coprococcus* spp., *Dorea formicigenerans*, and *Oribacterium* spp. [74]. Furthermore, another study noted an amelioration of GM dysbiosis in children with ASD [75]. Dietary supplementation with partially hydrolysed guar gum (PHGG) in ASD children increased the relative prevalence of *Acidaminococcus* and *Blautia*, whereas the relative prevalence of *Streptococcus*, *Odoribacter*, and *Eubacterium* decreased. Also, prebiotic intervention decreased the behavioural irritability of ASD children [75]. Two studies have been conducted examining the effect of prebiotic supplementation with a simultaneous effect on GM modulation in Parkinson's disease [76][77]. In the study of Becker et al. [77], an 8-week prebiotic intervention with resistant starch (RS) was conducted, enrolling 87 subjects distributed across three study arms: 32 PD patients who received RS, 30 control subjects who also received RS, and 25 PD patients who were provided with dietary instructions only. According to the results, a reduction in non-motor symptom load and a stable gut microbiome in PD patients after RS intervention were observed. In the study of Hall et al. [76], an open-label, non-randomised study was conducted in 10 newly diagnosed and 10 non-medicated and treated PD

participants, wherein the impact of 10 days of prebiotic (bar containing resistant starch and rice brain) intervention was evaluated. The prebiotic supplementation resulted in a reduction in the relative abundance of potentially pro-inflammatory bacteria, such as Proteobacteria and Escherichia coli, while increasing the relative abundance of SCFA-producing bacteria, including *Faecalibacterium prausnitzii*. In addition, the unified Parkinson's disease rating scale improved with prebiotic treatment [76]. The effects of prebiotic supplementation on schizophrenia were studied by Ido et al. [78]. More specifically, a female subject with schizophrenia was administered a prebiotic preparation of lactosucrose while keeping her medication unchanged. According to the results, after three months of lactosucrose administration, there was an improvement in psychotic symptoms, a significant decrease in the abundance of Clostridium, and an increased Bifidobacterium-to-Clostridium ratio [78].

More research is required to determine the effects of prebiotics in the management of neurological diseases. While there have been promising studies suggesting potential benefits, more comprehensive and long-term human research is needed to establish conclusive evidence.

Table 1. Main dysbiotic events that occur in GM during the onset and progression of neurological disorders.

Neurodegenerative Disease	Main Dysbiotic Events in GM	Reference
Autism spectrum disorder (ASD)	- Higher abundances of Bacteroides, Parabacteroides, Clostridium, Faecalibacterium, and Phascolarctobacterium and a lower relative abundance of Streptococcus and Bifidobacterium in ASD patients - Dysbiosis in ASD children may influence the development and severity of ASD symptomatology	[15][26][29]
Parkinson's disease (PD)	- Enrichment of the genera *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* and depletion of bacteria belonging to the *Lachnospiraceae* family and the *Faecalibacterium* genus in PD patients	[38][39]
Amyotrophic lateral sclerosis (ALS)	- Reduced ratio of *Firmicutes*/*Bacteroidetes*, decreased abundance of butyrate-producing *Oscillibacter*, *Anaerostipes*, *Lachnospira* counts, and *Prevotella*, increased abundance of glucose-metabolizing *Dorea* in ALS patients - GM composition alters during the course of the ALS	[51][53]

Neurodegenerative Disease	Main Dysbiotic Events in GM	Reference
Schizophrenia	- In the schizophrenia group, an enhanced count of bacterial families like *Prevotellaceae*, *Veillonellaceae*, *Bacteroidaceae*, and *Coriobacteriaceae* was observed compared to healthy controls, while *Ruminococcus* and *Roseburia* abundances were significantly lower in patients with schizophrenia - Specific bacteria may function as biomarkers to differentiate schizophrenia from healthy individuals - Differences in GM between remission and acute schizophrenia as well as between first-episode drug-naïve and chronically medicated schizophrenia patients	[60][62][63][64]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
Neurological diseases	Randomised, double-blind, placebo-controlled study	30 children diagnosed with ASD were categorised into two groups, A and B, based on their dietary habits. Group A consisted of children with unrestricted diets (n = 18), while Group B comprised those following an exclusion diet (n = 12). Subsequently, within each of these groups, children were assigned randomly to two feeding subgroups using a random number system. Group I	B-GOS® mixture (Bimuno®; Clasado Biosciences Ltd., Reading, UK) 1.8 g: 80% GOS content for a 6-week feeding period	Improvement in social behaviour scores	The administration of B-GOS led to modulation of the GM composition in autistic children following unrestricted diets. This modulation primarily affected bifidobacterial populations and also influenced other bacterial groups, including members of the *Lachnospiraceae* family such as *Coprococcus* spp., *Dorea formicigenerans*, and *Oribacterium* spp.	[74]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
		received a placebo, while Group II was administered B-GOS®				
	Cohort study	13 ASD children aged 4–9 years	Partially hydrolysed guar gum (6 g/day) for two months or longer	Decrease the behavioural irritability	The relative prevalence of *Acidaminococcus* and *Blautia* increased, whereas the relative prevalence of *Streptococcus*, *Odoribacter*, and *Eubacterium* decreased	[75]
	Open-label, non-randomised study	20 participants with PD, consisting of 10 newly diagnosed, non-medicated individuals with PD and 10 individuals who were already receiving treatment for PD	Prebiotics in the form of a bar containing resistant starch, rice bran, resistant maltodextrin, and inulin for 10 days (one bar = 10 g fibre)	Unified Parkinson's Disease Rating Scale improved with treatment	The consumption of prebiotics resulted in a reduction in the relative abundance of potentially pro-inflammatory bacteria, such as *Proteobacteria* and *Escherichia coli*, while increasing the relative abundance of bacteria known to produce SCFAs, including *Faecalibacterium prausnitzii*	[76]
	Monocentric, prospective, open-label clinical trial	The study included 87 subjects distributed across three study arms: 32 PD patients who received	5 g of resistant starch twice per day orally over a period of 8 weeks	Reduction in non-motor symptom load in the PD patients who received resistant starch	Stabilised faecal microbial diversity	[77]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
		resistant starch, 30 control subjects who also received resistant starch, and 25 PD patients who were provided with dietary instructions only				
		1 female subject with schizophrenia	A prebiotic preparation of lactosucrose (OligoOne®) 3.0 g/day was administered, with the medication unchanged	Improvement of psychotic symptoms	After three months of lactosucrose administration, there was a significant decrease in the abundance of *Clostridium* and an increased *Bifidobacterium* to *Clostridium* ratio. Additionally, improvements were observed in bowel movements, and there was a reduction in constipation	[78]
Liver diseases	Placebo-controlled, randomised pilot trial	14 individuals with liver-biopsy-confirmed NASH	The subjects were randomised to receive oligofructose (8 g/day for 12 weeks followed by 16 g/day for 24 weeks) or isocaloric placebo for 9 months	Prebiotic improved liver steatosis relative to placebo and improved overall NAS score	Oligofructose supplementation led to an increase in *Bifidobacterium* levels, while it resulted in a reduction of bacteria belonging to *Clostridium* cluster XI and I	[79]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
	Small cohort single-centre study	Twenty-four subjects with histologically confirmed liver cirrhosis and a body mass index (BMI) of 25.78 kg/m^2 were compared to 29 healthy controls	In the patient group, lactitol was administered orally at a dosage of 5 g three times daily, and samples were collected after four weeks of treatment	All clinical parameters, including MELD, showed no difference between pre- and post-lactitol treatment groups	After the lactitol intervention, there was an increase in the levels of health-promoting lactic acid bacteria, such as *Bifidobacterium longum*, B. *pseudo-catenulatum*, and *Lactobacillus salivarius*. Additionally, there was a significant decrease in the pathogen *Klebsiella pneumonia* and the associated antibiotic-resistant genes and virulence factors	[80]
Heart diseases	Randomised, placebo-controlled, double-blind cross-over trial	Untreated individuals with hypertension, being of either sex, 18–70 years of age, and having a BMI of 18.5–35 kg/m^2	Participants were initially assigned to either Diet A or Diet B for a duration of 3 weeks. Diet A included HAMSAB (prebiotic acetylated and butyrylated high amylose maize starch) administered at a daily dosage of 40 g, while Diet B consisted of a daily intake of 40 g	Reduction in ambulatory systolic blood pressure	HAMSAB intervention promoted the growth of the commensal bacteria *P. distasonis* and *R. gauvreauii* and supported the restoration of local production of SCFAs by these microbes	[81]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
			of a placebo over the same 3-week period. After a 3-week washout period, participants switched to the opposite diet arm for another 3 weeks			
Kidney diseases	Double-blind, parallel, randomised, placebo-controlled trial	20 patients with end-stage CKD undergoing haemodialysis	The participants were randomised to two groups: one received biscuits containing 20 g/d of high-amylose maize-resistant starch type 2 (HAM-RS2), an insoluble, fermentable fibre, while the other received regular wheat flour (placebo) for the first month and 25 g/d during the second month	Decrease in in systemic inflammation (serum urea, IL-6, TNFα, and malondialdehyde)	Supplementation of amylose-resistant starch, HAM-RS2, in patients with CKD led to an increase in *Faecalibacterium*	[82]
	Randomised controlled clinical trial	32 patients with CKD in stages 3 and 4 were recruited and randomly	Patients in intervention group received 30 mm lactulose syrup three	Creatinine significantly decreased in intervention group	Lactulose administration increase faecal *Bifidobacteria* and *Lactobacillus*	[83]

Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
		assigned to intervention (n = 16) and control (n = 16) groups	timesa day for an 8-week period. Control group received placebo 30 mm three times a day		counts in CKD patients	
	Randomised, double-blind, placebo-controlled, crossover study	12 patients undergoing haemodialysis	Patients were randomised to consume inulin (10 g/d for females; 15 g/d for males) or maltodextrin (6 g/d for females; 9 g/d for males) for 4 weeks, with a 4-week washout period	Inulin did not reduce faecal p-cresol or indoles, or plasma concentrations of p-cresyl sulphate or indoxyl sulphate	Inulin increased the relative abundance of the phylum *Verrucomicrobia* and its genus *Akkermansia*. In addition, inulin and maltodextrin resulted in an increased relative abundance of the phylum *Bacteroidetes* and its genus *Bacteroides*	[84]
	Randomised single-centre, single-blinded control trial	59 predialysis participants with CKD in stages 3 to 5 were randomised	59 participants were randomised to either the β-glucan prebiotic intervention group (13.5 g of β-glucan prebiotic fibre supplement containing 6 g of fibre, of which 3 g was β-glucan per serving) daily (n = 30) or the control group (n =	Supplementation of β-glucan fibre resulted in reduced plasma levels of the free fraction of colon-derived uremic toxins, without a change in kidney function over the 14-week study period	High prevalence of *Bacteroides* 2 in the CKD population	[85]

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Disease	Study Design	Population	Prebiotic Compound	Effects on the Disease	Beneficial Effects on GM	Reference
			29) for 14 weeks			

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