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REVIEW

Parkinson's disease and the gastrointestinal microbiome

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Abstract

Recently, there has been a surge in awareness of the gastrointestinal microbiome (GM) and its role in health and disease. Of particular note is an association between the GM and Parkinson's disease (PD) and the realisation that the GM can act via a complex bidirectional communication between the gut and the brain. Compelling evidence suggests that a shift in GM composition may play an important role in the pathogenesis of PD by facilitating the characteristic ascending neurodegenerative spread of α-synuclein aggregates from the enteric nervous system to the brain. Here, we review evidence linking GM changes with PD, highlighting mechanisms supportive of pathological α-synuclein spread and intestinal inflammation in PD. We summarise existing patterns and correlations seen in clinical studies of the GM in PD, together with the impacts of non-motor symptoms, medications, lifestyle, diet and ageing on the GM. Roles of GM modulating therapies including probiotics and faecal microbiota transplantation are discussed. Encouragingly, alterations in the GM have repeatedly been observed in PD, supporting a biological link and highlighting it as a potential therapeutic target.

Keywords Parkinson's disease · Gastrointestinal microbiota · Gastrointestinal microbiome · Gut dysbiosis · Biomarker · Medications

Introduction

Parkinson's disease (PD) is an incurable and progressive neurodegenerative disorder, affecting 1–2 per 1000 (0.4–2.0% of people above the age of 65) of the population worldwide [1]. PD is a multisystem disorder that contributes to significant morbidity and healthcare burden [2, 3]. It is predominantly associated with the irreversible degeneration of dopaminergic neurons in the substantia nigra and other brain regions [4], often characterised by widespread Lewy body (LB) formation in the central and peripheral nervous systems. Features characteristic of clinical disease include tremor, rigidity, bradykinesia and postural instability [5]. Premotor and non-motor symptoms of PD include

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constipation, hyposmia, REM-sleep behaviour disorder (RBD), as well as cognitive, neuropsychiatric, autonomic and sensory disturbances [6]. These symptoms can emerge years, or even decades, prior to the manifestation of motor symptoms, but often go unrecognised [7].

Recently, the human gastrointestinal microbiome (GM) has been proposed to be an integral link for the pathogenesis of many neurodegenerative diseases [8]. Evidence exists for a bidirectional interaction between the GM and the central nervous system (CNS), known as the 'microbiota–gut–brain axis' (MGBA) [9]. Multiple MGBA pathways exist, including microbially produced molecules with neuroendocrine activity (e.g. serotonin, gamma-aminobutyric acid) [10] and CNS-regulated physiological functions, such as intestinal motility influence on the microbial ecosystem [11]. These connections create a feedback loop between human physiological and microbial community states, forming the basis for neurodegenerative diseases of dysbiosis. Consequently, dysbiosis of the GM portrays an interesting lead to explore the pathogenesis of PD [12, 13] and presents as a novel diagnostic and therapeutic target [14].

The human gastrointestinal microbiome

The human GM contains in the order of 1×10^{14} bacteria [15], with a biomass comparable to the human brain at 1–2 kg [16]. The GM predominantly comprises bacteria, but also archaea, fungi, viruses and other simple eukaryotic organisms [8]. However, the metabolic activity of the GM is overwhelmingly dominated by bacteria. Their primary role is to anaerobically breakdown carbohydrates that are incompatible with human digestive processes. Other cellular microbes contribute other specific metabolic activities (e.g. methanogenesis by archaea) and bacteriophage viruses modulate the genetic background of bacterial growth in the gastrointestinal tract.

Establishment of the GM begins at birth and is vital for postnatal immune and enteric nervous system (ENS) development [17]. The GM also forms an integral defence barrier against potentially hazardous external stimuli and is highly adaptive with regard to changes in diet, lifestyle and the surrounding environment [18]. Diet, exercise, probiotic supplements and changes in hygiene can modify the composition of the GM [19], as can recolonisation following antibiotics and invasive pathogenic colonisation [20]. Despite constant environmental variation in the gut, the GM composition remains relatively stable during adulthood [21]. Although in some instances, dietary changes have been shown to induce variability over 3–4 days [22].

Gut microbiome and the nervous system

The MGBA connects the gastrointestinal tract to the CNS [23, 24], with neurosynaptic pathways of the vagal nerve, autonomic and enteric fibres, in addition to various neuroendocrine and neuroimmune pathways, mediating its integrity [25]. Under physiological conditions, the MGBA is a major participant in signalling pathways that regulate digestive function and metabolic homeostasis. However, various mechanisms that disrupt these pathways can perturb cognition, behaviour, learning, pain and neuropsychiatric features (including anxiety, depression and even neurodevelopmental disorders, such as autism) [15, 26–28]. It has been suggested that dysregulation of the MGBA may directly influence PD pathogenesis, with progressive neurodegeneration from the gut to the brain occurring as a consequence of ascending alpha-synuclein (α-Syn) aggregation and LB formation (Fig. 1) [29].

The GM influences neuronal network health and activity by facilitating the absorption of nutrients, vitamins and medications, as well as modulating the immune system [30] and moderating neurotoxic compounds (e.g. ammonia and D-lactate) [31]. It is also independently capable of neurotransmitter synthesis, including dopamine, noradrenaline, serotonin and the neuromodulators γ-aminobutyric acid and short-chain fatty acids (SCFAs) [10, 32–34]. These neurotransmitters act to modulate blood flow, affect gut motility and nutrient absorption, as well as supporting the gastrointestinal innate immune system [35]. As an example, dopamine synthesis in the brain is mediated by catecholamine-producing enzymes that are governed by the GM via the MGBA, producing half of the body's required dopamine [36]. Accordingly, this intricate network shares a crucial role in maintaining the vital physiological interplay between the gastrointestinal tract and the brain [37].

Braak's hypothesis for Parkinson's disease

Common clinical features of gastrointestinal dysfunction in PD include abnormal salivation, dysphagia, nausea, impaired gastric emptying and constipation, and occur in 80% of patients [30, 38]. Several large population studies have shown that constipation can precede motor symptoms of PD by up to 20 years, and increases the risk of developing PD [39, 40]. Consistent with the clinico-epidemiological observations, several neuropathological studies have found early accumulation of LBs in the ENS and dorsal motor nucleus of the vagus, with correlations to motor and gastrointestinal symptom severity [41, 42].

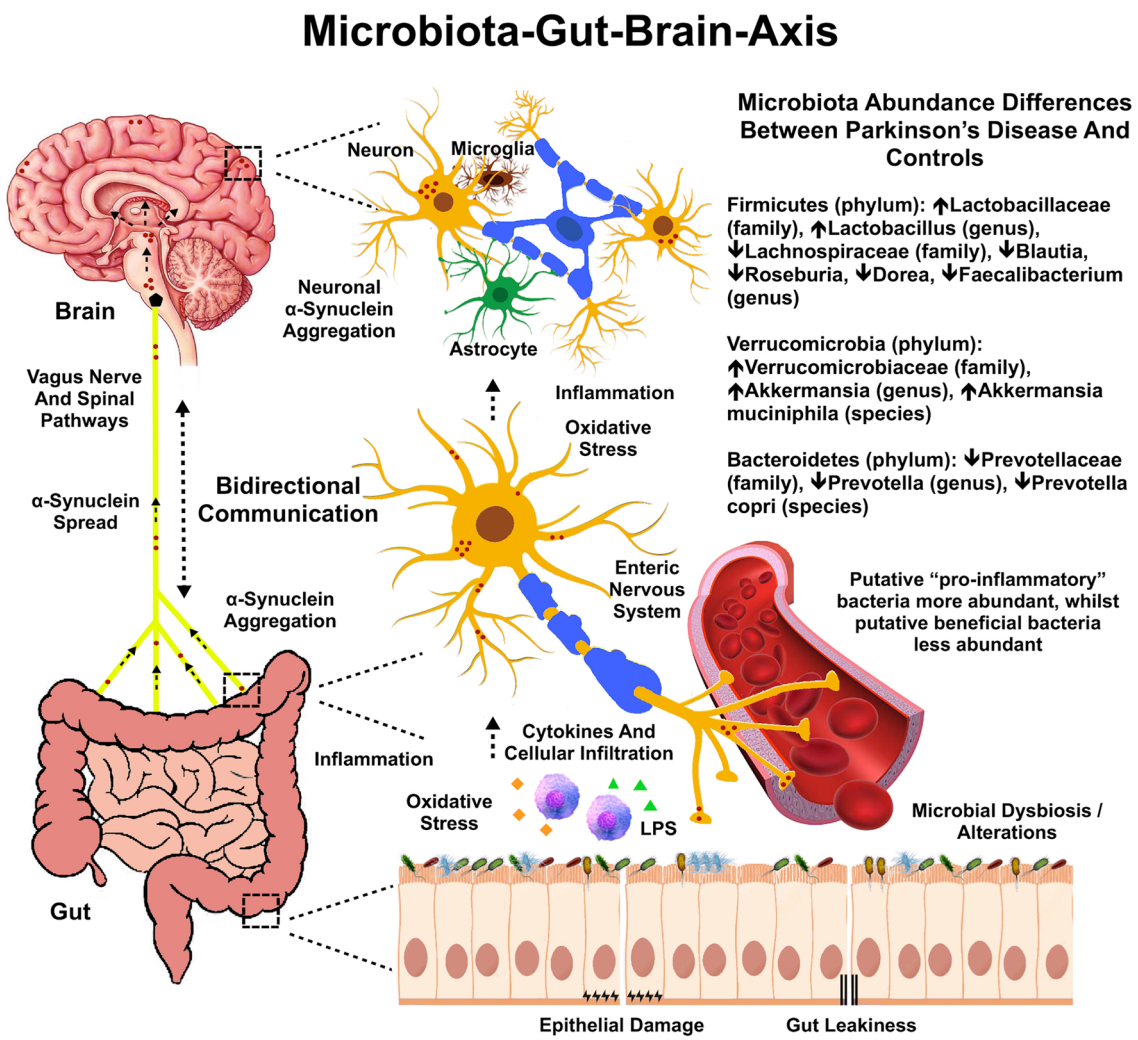

Fig. 1 The microbiota–gut–brian axis. Likely implicated pathways in the pathogenesis of Parkinson's disease. The microbiota–gut–brain axis provides a bidirectional communication between a dysbiotic gastrointestinal microbial population, characterised by increased inflammophiles and the central nervous system, via projections of the vagal nerve, as well as autonomic and enteric fibres. Abnormal changes in microbial metabolites, namely SCFAs, as well as the activation of innate immunity via pro-inflammatory cytokines propagate local inflammation, oxidative stress and increased mucosal permeability, facilitating leakage of bacterial products into the systemic circulation. These processes lead to abnormal enteric nervous system α-synuclein deposition and subsequent prion-like spread to the central nervous system, supported by ongoing activated microglial activity and systemic immune responses

Braak and colleagues proposed a "dual-hit hypothesis", where α-Syn aggregation commences outside of the brain, within the ENS and olfactory bulb, precipitated by external insults such as toxins and/or microorganisms [43]. They suggested that neuronal α-Syn deposition occurs in a caudorostral gradient, affecting the dorsal motor nucleus of the vagus nerve before progressing to the dopaminergic neurons of the substantia nigra [43]. However, this hypothesis remains controversial, as some studies were unable to replicate the caudorostral progression [44, 45]. Despite this, in support of Braak's findings, α-Syn has been shown to exhibit prion-like properties, with the ability to misfold, form aggregates and propagate from cell to cell [46, 47]. Further evidence from follow-up cohort studies in Danish [48] and Swedish [49] populations showed that only a full truncal vagotomy could decrease the risk of developing PD compared to a control population. The level of significance was further diminished when the dataset was analysed by an independent research group [45, 50]. In addition, hemivagotomy in a PD mouse model prevented α-Syn accumulation in the ipsilateral dorsal motor nucleus of the vagus [51]. Interestingly, a recent large Swedish database study suggested those with an appendectomy early in life had a 20% reduced risk of developing PD [52]. Despite these findings, phosphorylated α-Syn accumulation in the intestine is not a specific hallmark of PD, having been observed in patients with Lewy body dementia, Alzheimer's with Lewy bodies and

asymptomatic controls [53]. Thus, what constitutes pathological α-Syn species in the gut remains ill defined [54].

Inflammation and gut permeability

A critical aspect of host–microbiome interaction is the barrier functions of the gut epithelium [55]. Disruption of the barrier can trigger positive feedback loops involving intestinal inflammation, reactive oxygen/nitrogen species in the gut lumen and a shift in microbial composition favouring inflammophiles [56, 57]. Key to aberrant GM influence through the MGBA is destabilisation of the protective gastrointestinal barrier, resultant of translocation of bacteria or their products, such as lipopolysaccharides. This leads to oxidative stress and intestinal inflammation, which induces increased mucosal permeability [30, 58], as well as α-Syn aggregation in the ENS [59–61].

Intestinal permeability or 'gut leakiness' has been shown to be increased in PD patients compared to healthy controls [62–64] and mouse models of PD [65], correlating with an increase in enteric α-Syn deposition and tissue oxidative stress [62]. However, findings suggestive of increased intestinal permeability in PD require cautious evaluation. For example, Clairembault et al. [55] showed that the intestinal epithelial barrier was morphologically altered in PD but showed no change in the permeability of the intestinal epithelial barrier. Despite this, other disorders known to have increased intestinal permeability, such as inflammatory bowel disease, have recently been associated with an increased risk of PD. This further supports a role for gastrointestinal inflammation in the development of PD [66–68]. Moreover, priming of the gastrointestinal innate immune system by the GM can strengthen the inflammatory response to α-Syn [11].

Microbes vary in their cell structure and propensity to initiate pattern-recognition receptor signalling pathways, leading to inflammation. Evidence suggests that increased levels of *Escherichia coli* [62] and the proteobacteria *Ralstonia* [69], as well as lower plasma lipopolysaccharide-binding protein [70], reflect higher endotoxin exposure and drive intestinal inflammation. This inflammation is characterised by increased expression of the pro-inflammatory cytokines TNF-alpha, IFN-gamma, IL-6, and IL-1 beta, as well as an increased activation of enteric glial cells, consistent with colonic biopsies of PD patients [60]. Moreover, Perez-Pardo et al. [71] suggested that toll-like-receptor-4 signalling pathways may be implicated in facilitating intestinal inflammation, disrupting the intestinal barrier and facilitating neuroinflammation, as shown in PD patients and a PD mouse.

Further, SCFAs (acetate, propionate and butyrate) are major metabolic products of the GM, with lower faecal SCFA concentrations reported in PD patients compared to healthy controls [72]. SCFAs have multiple impacts, with nutritional and signalling roles being especially important in humans [73]. In particular, butyrate is a major energy substrate for colonocytes, playing an important role in gut health processes, such as mucin production and tight-junction formation [74]. Beyond their nutritional role, SCFAs are also a primary target for several G protein-coupled receptors that feed into immunometabolic regulatory circuits. The relative concentration and distribution of SCFA types have profound influence over gut function and homeostatic processes.

Several studies have indicated a decreased abundance of *Lachnospiraceae* in PD patients [69, 75, 76], known for their abundant production of SCFAs. Sampson et al. [77] suggested that SCFAs were a major factor inducing microglial activation and accelerating α-synucleinopathy in mouse models, thus enhancing PD pathophysiology [78]. However, depletion of SCFA-producing organisms in the gut has been observed in a variety of other conditions, suggesting this may be a marker of illness or associated with ageing [72], rather than a specific cause or biomarker of PD [75]. Consistently, controversy remains over the validity of decreased SCFAs leading to a pro-inflammatory gut environment in PD [78].

Gut infections in Parkinson's disease

The role of *Helicobacter pylori* in gastritis and dyspepsia is well known. However, in PD, it also appears to be associated with greater severity of motor features [79]. Several studies have suggested that antimicrobial treatment for *H. pylori* could improve PD motor symptoms and motor response complications, as well as levodopa absorption and bioavailability [80]. However, a Cochrane review concluded that current evidence remained insufficient to recommend *H. pylori* eradication in PD, due to a lack of informative clinical trials [81]. The prevalence of small intestinal bacterial overgrowth is estimated to range from 25–54% in PD [82, 83] and is associated with worse motor severity [83], longer daily off times and more episodes of delayed-on and dose failures [84]. A small-randomised controlled trial suggested that small intestinal bacterial overgrowth eradication in PD could result in improved motor fluctuations, without affecting the pharmacokinetics of levodopa [84].

Associations between gastrointestinal microbiota community structure and Parkinson's disease

Over the last 4 years, there have been numerous studies exploring the association between GM and PD, stimulated by greater awareness of gastrointestinal dysfunction in prodromal and early PD, as well as a better understanding of the MGBA [85, 86]. To date, 14 mainly cross-sectional

studies from seven countries in the northern hemisphere have reported GM alterations in PD [12, 13, 69, 70, 72, 75, 76, 87–93]. At the level of taxonomic profiles, no obvious recurrent pattern is seen in these studies. However, emerging trends show correlations between GM alterations in PD and a variety of motor and non-motor symptoms [94]. Considerable variabilities in the patient inclusion/exclusion criteria, molecular, bioinformatic and statistical methodologies between the studies were apparent and are summarised in Table 1. Most studies employed bacterial 16S ribosomal DNA amplicon sequencing of different variable regions to identify bacterial groups/genera/species, with three studies using targeted quantitative PCR to analyse preselected bacterial taxa, and one utilised metagenomic shotgun sequencing. PD patient cohort sizes ranged from 24 to 197 individuals, with all but one study comparing to a healthy control group. Exclusion of participants for use of antibiotics within 1 month of sample collection was generally observed. Only one study reported on longitudinal GM differences with a comparison at 2-year follow-up in 28 patients [13].

Each of the studies found significant differences between PD and healthy control groups, and collectively showed significant differences in the overall faecal GM composition in PD patients when compared to non-PD controls. In spite of this, it is not certain whether these changes are the cause or consequence of the gastrointestinal dysfunction associated with PD. Recent evidence from Heintz-Buschart et al. [88] suggests that GM alterations likely pre-date the motor symptoms of PD. The highest number of microbiota abundance differences between PD and controls was reported in the phylum *Firmicutes* [95], the largest phylum in the human GM. Specifically, increased *Lactobacillaceae* (family) and *Lactobacillus* (genus) and decreased *Lachnospiraceae* (family), *Blautia*, *Roseburia*, *Dorea* and *Faecalibacterium* (genus) were observed. The most consistent differences were reported in the phylum *Verrucomicrobia*, principally increased *Verrucomicrobiaceae* (family), *Akkermansia* (genus) and *Akkermansia muciniphila* (species). Moreover, significant changes in abundance of the phylum *Bacteroidetes* were also reported, with reductions in *Prevotellaceae* (family), *Prevotella* (genus) and *Prevotella copri* (species) (Table 1). Some studies deduced that putative "pro-inflammatory" bacteria were significantly more abundant, while putative beneficial bacteria were less abundant in PD [69].

Several studies have evaluated predicted functional differences based on faecal GM metagenomic data and suggested alterations of several metabolic pathways in PD, when compared to non-PD controls [69, 75, 91]. Kershavarzian et al. [69] showed that a large number of genes involved in metabolism were significantly lower in the PD faecal microbiome, whereas genes involved in lipopolysaccharide biosynthesis and type III bacterial secretion systems were significantly higher in PD patients. Hill-Burns et al. [75] found alterations in pathways involved in carbohydrate, energy, lipid, cofactor, vitamin and xenobiotic metabolism, as well as xenobiotics. The only study that utilised a very comprehensive metagenomics shotgun analysis found differences in microbiota metabolism in PD involving the β-glucuronate and tryptophan metabolism pathways [91]. Furthermore, metabolite studies reported reduced levels of serum lipopolysaccharide-binding protein [70, 96] and faecal SCFA [72] in PD patients.

Evaluating atypical parkinsonism, Barichella et al. [76] suggested the overall gut microbiota composition in multiple system atrophy (MSA) and progressive supranuclear palsy were not significantly distinct when compared to PD. Moreover, changes in several bacteria taxa when compared to controls were similar to PD [76], whilst drug-naïve PD patients had lower abundances of *Lachnospiraceae* when compared to controls [76]. In another MSA GM study, higher relative abundances of Gram-negative, putative 'pro-inflammatory' bacteria from the phylum *Bacteroidetes* and *Proteobacteria* were noted in faecal and mucosal samples, whilst putative 'anti-inflammatory' butyrate-producing bacteria were less abundant. Further, the relative abundance of a number of genes involved in metabolism were lower in faecal material from patients with MSA, whilst the relative abundance of genes involved in lipopolysaccharide biosynthesis were higher in MSA patients compared to healthy controls [97]. Several bacteria taxa have been associated with various motor response complications and worse motor severity in PD (Table 2).

Significant differences were also found in the GM composition of sigmoid mucosa in PD when compared to controls, although differences were more pronounced in faecal versus mucosal samples [69]. Comparison of nasal microbiota between PD patients and controls did not yield significantly different results, limiting the utility of a nasal microbiota biomarker in PD [88, 98]. One study on oral microbiota found significant differences in overall composition between PD patients and controls and, interestingly, a higher abundance of *Prevotellaceae* in PD, contrary to the previous findings in the faecal microbiome [98]. Lastly, increased abundance of *Anaerotruncus* and reduced relative abundance of *Prevotellaceae* were shown in patients with idiopathic RBD, suggesting a possible prodromal GM change in PD [88].

Of great interest is the pioneering work by Samson and colleagues [77], who have provided the strongest evidence to date for a causal role of GM alterations in PD. These investigators showed that transplantation of gut microbiota from six PD patients to transgenic mice overexpressing α-Syn resulted in worsening of clinically relevant motor. Additionally, mice raised in a germ-free environment developed little PD-related pathophysiology, including motor dysfunction, neuroinflammation and α-Syn pathology [77]. They hypothesised that the clinical effects of gut microbiota were

Table 1 Summary of studies evaluating the gut microbiota in Parkinson's disease

Cross-sectional studies	Geographic region	Sample size ($n=$)	Sequencing	Differences at family level		Differences at genera level	
			Untargeted	Over-represented in PD cases	Over-represented in healthy controls	Over-represented in PD cases	Over-represented in healthy controls
Barichella et al. [76]	Italy (Milan)	193 PD (39 drug naïve), 22 PSP, 22 MSA and 113 controls	V3-V4 16S rRNA gene sequencing Illumina MiSeq	*Verrucomicrobiaceae*, *Enterobacteriaceae*, *Christensenellaceae*, *Lactobacillaceae*, *Coriobacteriaceae*, *Bifidobacteriaceae*	*Lachnospiraceae*	*Akkermansia, Parabacteroides, Ruminococcus*, *Oscillospira*	*Roseburia*
Lin et al. [93]	China (Guangdong)	75 PD and 45 controls	V4 16S rRNA gene sequencing Illumina HiSeq	*Bifidobacteriaceae, Eubacteriaceae*, *Aerococcaceae*, *Desulfovibrionaceae*	*Lachnospiraceae*, *Pasteurellaceae*, *Streptococcaceae*, *Methylobacteriaceae*, *Comamonadaceae*, *Halomonadaceae*, *Hyphomonadaceae*, *Brucellaceae*, *Xanthomonadaceae*, *Actinomycetaceae*, *Sphingomonadaceae*, *Micrococcaceae*, *Intrasporangiaceae*, *Methanobacteriaceae*, *Idiomarinaceae*, *Brevibacteriaceae*, *Gemellaceae*		
Qian et al. [90]	China (Shanghai)	45 PD and 45 controls	V3-V4 16S rRNA gene sequencing Illumina MiSeq			*Clostridium IV*, *Aquabacterium*, *Holdemania*, *Sphingomonas*, *Clostridium XVIII*, *Butyricicoccus*, *Anaerotruncus*	
Heintz-Buschart et al. [88]	Germany (Kassel)	76 PD and 78 controls	V4 region 16S rRNA gene sequencing and whole metagenome shotgun sequencing Illumina HiSeq	*Verrucomicrobiaceae*		*Akkermansia*, *Clostridium XIVb*, *Anaerotruncus*	
Hill-Burns et al. [75]	USA (Seattle, Atlanta, New York)	197 PD and 130 controls	16S rRNA gene sequencing Illumina MiSeq	*Bifidobacteriaceae, Lactobacillaceae*, *Tissierellaceae*, *Christensenellaceae*, *Verrucomicrobiaceae*	*Lachnospiraceae, Pasteurellaceae*	*Bifidobacterium, Lactobacillus*, *Akkermansia*	*Blautia*, *Roseburia*, *Faecalibacterium*

Table 1 (continued)

Cross-sectional studies	Geographic region	Sample size (n =)	Sequencing	Differences at family level		Differences at genera level	
			Untargeted	Over-represented in PD cases	Over-represented in healthy controls	Over-represented in PD cases	Over-represented in healthy controls
Li et al. [87]	China (Beijing)	24 PD and 14 controls	V3-V5 16S rRNA gene sequencing Illumina MiSeq	*Enterobacteriaceae, Veillonellaceae, Erysipelotrichaceae, Coriobacteriaceae, Streptococcaceae, Moraxellaceae, Enterococcaceae*		*Acidaminococcus, Acinetobacter, Enterococcus, Escherichia–Shigella Megamonas, Megasphaera, Proteus, Streptococcus*	*Blautia, Faecalibacterium, Ruminococcus*
Bedarf et al. [91]	Germany (Bonn)	31 PD and 28 controls. Male patients only	Metagenomic shot gun sequencing Illumina HiSeq			*Akkermansia,* Unclassified Bacteria, Unclassified *Firmicutes*	*Prevotella, Eubacterium*
Hopfner et al. [92]	Germany (Kiel)	29 PD and 29 controls	V1-V2 16S rRNA gene sequencing Illumina MiSeq	*Lactobacillaceae, Barnesiellaceae, Enterococcaceae*			
Petrov et al. [101]	Russia (Tomsk)	89 PD and 66 controls	V3-V4 16S rRNA gene sequencing Illumina MiSeq			*Christensenella, Catabacter, Lactobacillus, Oscillospira, Bifidobacterium*	*Dorea, Bacteroides, Prevotella, Faecalibacterium*
Keshavarzian et al. [69]	USA (Chicago)	38 PD and 34 controls	V4 16S rRNA gene sequencing Illumina MiSeq	Faecal *Bacteroidaceae, Clostridiaceae, Verrucomicrobiaceae*	Faecal *Lachnospiraceae, Coprobacillaceae*	Faecal *Bacteroides, Oscillospira, Akkermansia*	Faecal *Ie Blautia, Coprococcus, Dorea, Roseburia*
				Mucosal *Oxalobacteraceae*	Mucosal *Coprobacillaceae*	Mucosal *Ralstonia*	Mucosal *Faecalibacterium, Dorea*
Scheperjans et al. [12]	Finland (Helsinki)	72 PD and 72 controls	V1–V3 16S rRNA gene sequencing Roche Pyrosequencing	*Lactobacillaceae, Verrucomicrobiaceae, Bradyrhizobiaceae, Clostridiales*	*Prevotellaceae*		

Table 1 (continued)

			Targeted	Over-represented in PD cases	Over-represented in healthy controls	Over-represented in PD cases	Over-represented in healthy controls
Unger et al. [72]	Germany (Herborn)	34 PD and 34 controls	Quantitative PCR of targeted bacterial groups	*Enterobacteriaceae*	*Prevotellaceae*	*Akkermansia muciniphila*, *Bifidobacterium*	*Faecalibacterium prausnitzii*, *Lactobacillaceae*, *Enterococcaceae*
Hasegawa et al. [70]	Japan (Nagoya)	52 PD and 36 controls	Quantitative RT-PCR of 16S or 23S rRNA of 19 bacterial groups			*Lactobacillus*	*Clostridium coccoides*, *Clostridium leptum*, *Bacteroides fragilis*

Longitudinal studies	Geographic region	Sample size (n=)	Sequencing	Differences at family level	Differences at genera level	
			Targeted		Over-represented in PD cases	Underrepresented in PD cases
Minato et al. [13]	Japan (Nagoya)	28 PD. No controls. 2 year follow up	Quantitative RT-PCR of 16S or 23S rRNA of 19 bacterial groups			*Bifidobacterium, Bacteroides fragilis*, *Atopobium*, *Bifidobacterium* associated with various motor and non-motor features

Table 2 Clinical correlations of gut microbiome changes in Parkinson's disease

	Clinical effect	Alteration in the gastrointestinal microbiome
Motor features	Postural instability and gait difficulty phenotype	Correlated with the relative abundance of *Enterobacteriaceae* [12]
	Motor complications	Positively associated with *Aquabacterium*, *Peptococcus* and *Sphingomonas* [90], whilst *Anaerotruncus* spp., *Clostridium XIVa* and *Lachnospiraceae* were correlated with (MDS-UPDRS) part III scores [88]
	Changes in the Unified Parkinson's Disease Rating Scale Scores	Predicted by lower counts of *Bifidobacterium* and *Atopobium* [13]
	Worse clinical phenotype, i.e. higher frequencies of postural instability, gait disturbance and cognitive impairment	Decreased abundances of *Lachnospiraceae* and increased *Lactobacillaceae* and *Christensenellaceae* [76]
Non-motor symptoms	Depression	Altered abundance of *Anaerotruncus* spp. [88]
		Higher relative abundance of *Christensenella minuta*, *Clostridium disporicum* and *Oscillibacter valericigenes* [101]
	Anxiety	Higher abundance of *Clostridium clariflavum* [101]
	Cognition (assessed by the mini mental state examination)	Positively associated with the genera *Butyricicoccus* and *Clostridium XIVb* [90]
	Hallucinations and delusions	Lower counts of *Bifidobacterium* [13]
	Idiopathic rapid eye movement sleep behaviour disorder (not-yet clinically diagnosed Parkinson's disease patients)	Increased abundance of *Anaerotruncus* and reduced relative abundance of *Prevotellaceae*, suggesting a possible prodromal gut microbiome change in Parkinson's disease [88]
Medication effects	Catechol-*O*-methyltransferase inhibitors/anticholinergics	Increased abundances of *Lactobacillaceae* and reduced *Clostridiales Incertae Sedis IV* [75]
	Catechol-*O*-methyltransferase inhibitors	Decreased abundances of *Firmicutes, Lachnospiraceae* and *Ruminococcaceae*, whilst increased abundances of *Actinobacteria*, *Porphyromonadaceae*, *Lactobacillaceae* and *Proteobacteria* [76]
	Levodopa	Associated with the abundances of *Bacillaceae* [88]
	Levodopa equivalent daily dose	Negatively associated with *Dorea* and *Phascolarctobacterium* [90]

primarily mediated by SCFAs, enabling the activation of microglia and potentially leading to increased neuroinflammation and subsequent exacerbation of PD. Furthermore, they demonstrated that the oral administration of SCFAs in a germ-free PD mouse model resulted in prominent motor symptoms [77].

Non-motor symptoms and the gastrointestinal microbiota

Non-motor symptoms (NMS) generally pre-date motor features in PD, reflecting degeneration of extra-nigral areas prior to involvement of the substantia nigra. Common NMS include disrupted sleep architecture (particularly with RBD), impaired olfaction, behavioural changes, as well as impaired visuospatial abilities and executive function [99]. There is growing evidence of altered GM composition in various PD-related NMS, in addition to other psychiatric disorders, namely anxiety and depression, which are highly prevalent in PD [100]. Recently, it was identified that changes in *Anaerotruncus*, *Akkermansia* and several other unclassified bacteria were significantly related to NMS according to MDS-UPDRS part I [88] (Table 2). For instance, an altered abundance of *Anaerotruncus* spp. was related to depression in PD [88] and patients with anxiety had a higher abundance of *Clostridium clariflavum* compared to those without anxiety [101]. Furthermore, those with moderate depression were suggested to have higher relative abundance of *Christensenella minuta*, *Clostridium disporicum* and *Oscillibacter valericigenes* compared to those without depression or with mild depression [101]. In other PD studies, depression was also associated with the genera *Anaerotruncus* spp. [88]. Studies outside of PD have identified significant changes in the GM composition in those with depression. Depression and PD frequently coincide, with depression often

contributing significantly to impairment of health-related quality of life in PD [102]. Jiang et al. [103] showed that those who were acutely depressed had higher levels of *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*, and lower levels of *Firmicutes*; a negative correlation between *Faecalibacterium* and the severity of depression was also described.

Gastrointestinal symptoms are one of the most common PD NMS, involving the entirety of the gastrointestinal tract and evident throughout the whole disease course [104]. Patients with PD and irritable bowel syndrome (IBS)-like symptoms have been shown to feature more NMS, as well as a lower faecal abundance of *Prevotella* bacteria than those without IBS-like symptoms [86]. Constipation, a cardinal NMS of PD, has also been shown to predispose to GM alterations, along with increased mucosal permeability and inflammation [105]. Cognitive changes have been linked to varied GM compositions in PD, with positive associations in the abundance of *Butyricicoccus* and *Clostridium XIVb* described [90]. In a 2-year longitudinal study, lower counts of *Bifidobacterium* and *Bacteroides fragilis* at baseline were associated with worsening hallucinations and delusions, and worsening motivation and initiative [13], respectively.

Parkinson's disease medications and the gastrointestinal microbiome

An extensive range of medications have been proposed to influence the composition of the GM, including several PD medications [106]. One study reported that treatment with standard PD treatments, catechol-*O*-methyltransferase (COMT) inhibitors and anticholinergics, resulted in a difference in the composition of the GM, independent of the PD effect [75]. COMT inhibitor usage was also shown to be significantly associated with increased abundance of *Lactobacillaceae* and reduced abundance of *Clostridiales Incertae Sedis IV* [12]. The isolated effects of levodopa/carbidopa were difficult to identify due to ubiquitous usage by PD patients [75]. However, levodopa appeared to be significantly associated with *Bacillaceae* abundance in one study [88]. Qian et al. [90] suggested that the levodopa equivalent daily dose was negatively associated with the genera *Dorea* and *Phascolarctobacterium*. Furthermore, Bedarf et al. [91] commented that the use of monoamine oxidase inhibitors, amantadine or a dopamine agonist had no overall influence on taxa abundance or microbial function. Significantly, reduced abundance of *Prevotella*, reported by several PD–GM studies, could not be explained by PD medications, and was observed in levodopa naïve early-stage PD patients [91]. Importantly, other significant between-group differences in the GM were observed between drug-naïve and treated PD patients [69]. Interestingly, no studies have specifically evaluated the GM composition in advanced disease patients requiring device-assisted therapies, highlighting a need for more studies in pre-treated PD patients. Hopfner et al. [92] reported that in their cohort of 29 PD patients, six were treated with deep brain stimulation, although no GM subgroup analysis was provided.

Lifestyle influences and other potential confounders of the gastrointestinal microbiota in Parkinson's disease

There is increasing evidence that certain lifestyle factors contribute to PD pathology. Increased urate levels have been shown to provide a protective effect through antioxidant activity, conferring a 33% risk reduction for PD [107]. Furthermore, although debated, epidemiological studies suggest a smoking history may confer approximately 60% reduced risk of developing PD, whilst coffee consumption was found to reduce the risk by 30% [108, 109]. These neuroprotective effects are likely mediated through nicotinic acetylcholine and adenosine A(2A) receptor-mediated activity [30], or through prevention of α-Syn misfolding and fibril formation [110]. Derkinderen et al. [111] suggested that the beneficial effects of smoking and coffee consumption in PD risk could be mediated through the MGBA, specifically by altering the composition of the GM in ways that mitigate intestinal inflammation, thus reducing α-Syn misfolding and deposition. This hypothesis was supported by a study in humans showing gut dysbiosis after smoking cessation [112], with smokers having a higher abundance of faecal *Bacteroides* and *Prevotella*. After smoking cessation, a decreased abundance of *Proteobacteria* and an increased abundance of *Firmicutes* and *Actinobacteria* were observed [112].

Effects of coffee consumption may relate to its composition of alkaloids, phenolic compounds, fibres and minerals [30]. SCFAs that arise from coffee's dietary fibre metabolism may cause an expansion of *Bacteroides* and *Prevotella* bacteria [113]. Coffee consumption can also increase the abundance of anti-inflammatory *Bifidobacteria* and decrease *Clostridium* spp. and *Escherichia coli* [114, 115]. Furthermore, consumption of alcohol-containing products, coffee, tea and sugar-sweetened drinks show correlation with altered microbial compositions. For instance, red wine consumption correlates with an increased abundance of *F. prausnitzii*, known for its anti-inflammatory functions [116]. Furthermore, coffee, tea and red wine consumption have been associated with increased GM diversity [117], supporting lifestyle modification in the influence of PD predisposition.

Stress has also been suggested to promote gut leakiness and affect the microbiota community abundances in several animal and human studies [118, 119]. A recent study by Dodiya et al. [120] showed that stress exacerbated intestinal inflammation, gut leakiness, endotoxemia,

neuroinflammation and dopamine loss, in a PD mouse model.

Macronutrients, particularly carbohydrates, have also been shown to influence the composition and function of the GM [121]. For instance, individuals consuming more plant carbohydrates and fibre had a higher abundance of *Prevotella/Paraprevotella,* compared to those consuming predominantly animal fat and protein who harboured more of the *Bacteroides* enterotype [122]. Fibre-rich diets appear to enhance the growth of colonic bacteria producing SCFAs, which in turn confer systemic anti-inflammatory effects [72]. For instance, *Prevotella*, which has been shown at lower abundance in PD [12], is an important contributor to gut SCFA synthesis, as well as folate and thiamine biosynthesis [123], nutrients known to be deficient in PD [124].

Further, the Western diet is known to be high in refined carbohydrates and saturated fats, which may result in a dysbiotic GM, with lower *Bifidobacteria*, higher *Firmicutes* and *Proteobacteria* [125]. High-fat diets have also been shown to induce intestinal and systemic inflammation in animal models by increasing intestinal permeability and altering the GM [126]. Consumption of dairy products has been suggested to variably affect the risk of PD [109]. Drinking sour milk with a lower fat content has been associated with higher GM diversity of beneficial *Leuconostoc mesenteroides* and *Leuconostoc lactis*, whilst drinking whole milk was associated with lower diversity [116]. Furthermore, studies evaluating urate metabolism suggested that *Prevotella*-dominant enterotypes were associated with higher serum urate levels [12].

The effects of age and exercise have also been described in relation to the GM. Age-related changes in the GM reflect decreased diversity of species [127], with corresponding decreases in microbial functional abundance [116]. Biagi et al. [128] suggested that ageing was associated with increasing abundance of subdominant species, including rearrangement in their co-occurrence networks. A significant reduction in the abundance of *Lactobacilli, Bacteroides/Prevotella* and *Faecalibacterium prausnitzii* and an increased abundance of *Ruminococcus*, *Atopobium* and *Enterobacteriaceae* were reported in individuals with high frailty scores [129]. Elderly community-dwelling residents were noted to share a more diverse GM and were healthier compared to those in short or long-term residential care [130], reflected by greater inter-individual GM variation, as well as significant relationships between the GM, diet and differences between community and institutional living [131].

Exercise has also been associated with favourable changes in the GM composition, influencing energy homeostasis and regulation [132]. Physical exercise has been suggested to enhance the number of beneficial bacterial species, enrich microbial diversity and improve the development of commensal bacteria, irrespective of diet [132, 133]. Estaki et al. [133] found that fitter individuals had a GM enriched in butyrate-producing taxa, including *Roseburia, Clostridiales*, *Lachnospiraceae* and *Erysipelotrichaceae*, favouring optimal gut health and improved metabolism.

Antibiotics, not surprisingly, have been shown to induce significant changes in the GM, as well as in dopaminergic signalling [134]. Antibiotic therapy affects the diversity of the GM and is associated with reduced abundance of *Bifidobacteria*, as well as *Bacteroides* and *Prevotella* groups [130]. Minocycline has shown neuroprotective efficacy in PD animal models, by limiting nigrostriatal neurodegeneration, as well as blocking dopamine depletion in the striatum and nucleus accumbens [135]. Other studies have also suggested minocycline-related antioxidant and anti-inflammatory properties confer dopaminergic neuroprotection [136]. Minocycline has been further shown to re-balance GM dysbiosis in a hypertension model, by reducing the *Firmicutes*:*Bacteroidetes* ratio [137] although no studies have been conducted to directly evaluate minocycline's effect on the GM in PD patients [15]. Furthermore, minocycline is implicated in modulation of depression, likely due to anti-inflammatory properties and neuroprotective roles [138]. Conversely, minocycline has been suggested to have deleterious effects in PD animal models [139].

Other antibiotics, including ampicillin, ceftriaxone, neomycin, metronidazole and polymyxin B, have also shown potential neuroprotective mechanisms or result in clinical disease changes via MGBA interactions [15]. Potential mechanisms suggest decreased physical activity, as well as modulation of GM abundances, as potential considerations [140]. Despite these small, mainly animal-based studies describing interesting interactions with antibiotic use and the neurobiology of GM–PD, further human clinical trials are required to investigate potential antibiotic influences on the MGBA.

Potential roles of prebiotics and probiotics in Parkinson's disease

Emerging interest evaluating prebiotic and probiotic use in PD and other neuropsychiatric disorders is providing valuable insight into potential novel mechanisms aimed at favourably modifying various symptoms. Consumption of fermented milk containing *Lactobacillus casei* Shirota for 5 weeks was shown to improve stool consistency and reduce bloating and abdominal pain in patients with PD [141]. A more recent randomised controlled trial showed that intake of fermented milk containing probiotic strains and prebiotic fibre significantly increased the frequency of complete bowel movements in PD patients [142]. Probiotic studies have reported beneficial health effects by a variety of mechanisms, including enhancing intestinal epithelial integrity,

protecting against barrier disruption, stimulating a healthy mucosal immune system and suppressing pathogenic bacterial growth [143].

Human studies are beginning to show that probiotics may be effective in reducing depression and anxiety-like symptoms [144], with those receiving probiotics having higher numbers of faecal–gut microbial species and lowered levels of *Bacteroidaceae* compared to healthy controls [145]. Improving gastrointestinal function with probiotic supplementation may also potentially improve levodopa absorption [143], and reduce behavioural and cognitive deficits commonly observed in PD, such as anxiety, depression and memory problems [146]. Prebiotics, which include dietary soluble fibres, such as galactooligosaccharides or fructooligosaccharides, can stimulate the growth of intrinsic commensal microbiota and have also been keenly studied for their effects on mood [147]. Recent prebiotic studies have shown promising anxiety-modifying effects after consumption of certain dietary soluble fibres [148] and fermented foods [149], suggesting anxiolytic efficacy. Therefore, probiotic use and specific dietary modifications may provide useful treatment modalities for patients with PD, aiming to favourably modify the GM composition, by reducing ENS inflammation and α-Syn aggregation, whilst improving gastrointestinal function.

Controversies and future directions

Faecal microbiota transplantation (FMT) was described some 2000 years ago in China, in the treatment of human gastrointestinal disease [150]. FMT has been increasingly used in the treatment of resistant *Clostridium difficile* infection with excellent efficacy and safety [151, 152] and was more recently trialled in non-PD patients, with marked improvement of constipation [153]. However, little is known regarding its utility in PD, with only anecdotal reports of benefit [154]. Evolving interest exploring FMT in PD suggests a possible slowing of disease progression, coupled with potential change in diet and medication requirement, whilst repopulating the gastrointestinal tract with favourable microbiota [155]. Prospective longitudinal controlled trials are needed to validate the safety and efficacy potential of FMT for PD recipients. It is important to note, however, that neither pre/probiotics nor FMT appear to influence the core PD symptoms but, at best, may alter associated disease features such as anxiety, depression and, of course, constipation.

Further, the scope of gut dysbiosis in PD may be rather more complex and also reflect important changes in the gut virome, particularly inferred by bacteriophage viruses. A recent study by Tetz et al. [156] identified an increased abundance of *Lactococcus* bacteriophage in PD, impacting abundances of lactic acid bacteria, known to produce dopamine and regulate intestinal permeability. Ultimately, the GM may be utilised as an early and minimally invasive PD biomarker, something urgently needed to provide prodromal or preclinical diagnosis of PD. The most compelling results from across the PD–GM studies identify increased abundances of *Lactobacillaceae* (family), *Lactobacillus* (genus), *Verrucomicrobiaceae* (family), *Akkermansia* (genus) and reduced *Prevotellaceae* (family), *Prevotella* (genus), *Lachnospiraceae* (family), *Blautia*, *Roseburia*, *Dorea* and *Faecalibacterium* (genus) in PD patients [12, 13, 69, 70, 72, 75, 76, 87–93]. These findings suggest significant biological variations that need to be further explored by a meta-analysis evaluating the influence of confounders, such as geography and dietary variations, and whether a distinct and consistent GM pattern exists in PD. Furthermore, lowered *Prevotella* abundance is not entirely specific to PD, as other conditions including type I diabetes [157], colon cancer [158] and autism [159], also share reduced *Prevotella* abundances. Perhaps inversely, the elevated faecal abundance of *Prevotella* seen in several studies could be utilised as a useful biomarker to exclude PD. Interestingly, the canonical signature of GM dysbiosis, reflected by typically increased abundances of *Proteobacteria* bacteria [160], was not clearly shown across the PD–GM studies. Instead, increased abundances of *Akkermansia* were noted, requiring further evaluation by meta-analysis.

With expanding interest in the GM and neurodegenerative disorders, next-generation sequencing and high-throughput taxonomic classification will be an important approach to identify patterns of differing GM abundances. If coupled with faecal metabolic profiling, the combination of approaches may better identify useful biomarkers. By identifying disease discriminant biomarkers, faecal microbiota screening in the community may one day be utilised to identify individuals at risk of neurological dysfunction, as well as those with prodromal PD. It would be ideal for these clinical efforts to be complemented by well-designed preclinical models aiming to understand the causal link between the GM and PD. This could lead to the development of novel therapeutic approaches aimed at interfering with α-Syn aggregation and clearance [161–163].

Conclusion

Across the most recent GM studies in PD, changes in bacterial taxa have been repeatedly shown in association with disease, endorsing a plausible biological link between the GM and PD [164]. With increasing acceptance, it appears that these GM changes are implicated and contribute to PD pathology, rather than a mere consequence of PD-related gut dysfunction. The MGBA interactions are complex and require ongoing study, although evidence suggests that gut

mucosal integrity and permeability, SCFA metabolism, oxidative stress and inflammation are cardinal to the process [85]. Ultimately, these mechanisms support α-Syn aggregation within the ENS and subsequent caudorostral cell-to-cell α-Syn transfer, leading to advancing nigrostriatal dopaminergic network failure, with subsequent overt manifestation of disease. An improved understanding of the specific attributes and characteristics of the GM community structures in PD could lead to more targeted antimicrobial therapies and dietary interventions aimed at modulating the GM. However, the frontier is rapidly shifting and future research needs to challenge these observations by exploring such mechanisms that modulate the GM in PD, as a viable therapeutic strategy to slow or arrest the spread of disease. If such means are found, it could unravel a new wave of therapies that target the disease pathophysiology rather than just addressing symptomatic relief, providing a new direction in PD treatment that is urgently needed.

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Compliance with ethical standards

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