Neurodegenerative Diseases and the Gut Microbiota

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Abstract Neurodegenerative diseases are characterised by a progressive loss of neurons that leads to a range of cognitive and/or motor dysfunctions. During recent decades, some common pathways leading to neurodegeneration have been identified, such as protein misfolding, neuroinflammation, and the dysfunction of mitochondria and protein clearance systems. More recently, an altered gut microbiota has been identified as another potential feature seen in neurodegenerative disorders, which has been shown to play a central role in health and disease. The gut microbiota communicates with the central nervous system along the microbiota-gut-brain axis modulating host health and disease. Although the specific role of gut microbiota on the pathogenesis of these diseases is still under investigation, therapeutic approaches focusing on the modification of gut microbiota could bring novel therapeutics for neurodegenerative diseases.

Keywords Neurodegeneration · Alzheimer · Parkinson · Huntington · Inflammation · Protein misfolding · Mitochondria · Gut microbiota

1 Introduction

It's been over a century since James Parkinson and Alois Alzheimer first published their observations of the neurodegenerative diseases that bear their names [1, 2]. Today, neurodegenerative diseases are one of the main causes of comorbidity and mortality in older adult populations, and these numbers will likely increase with the proportion (or number) of aged individuals increasing day by day. These debilitating diseases have immense emotional and financial tolls on all societies worldwide.

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In broad terms, neurodegenerative diseases are conditions where neurons in the central or peripheral nervous system progressively degenerate, leading to central nervous system dysfunction. Several neurodegenerative diseases can be identified depending on the neuronal population affected, its localisation in the brain, and the clinical features observed (see Table 1). Most neurodegenerative diseases are characterised by depositions of misfolded native proteins and a widespread clinical symptomatology. The traditional method of classifying neurodegenerative disease is based on clinicopathological features from the anatomical area affected with the neuronal dysfunction supported by molecular pathology patterns of the misfolded proteins [14]. Nevertheless, classifying these diseases is a challenging subject as specific symptoms and protein aggregates can be found in multiple diseases, hampering the diagnosis of the disease [15]. Thus, the idea that neurodegenerative diseases are overlapping or even a continuum has been raised [14].

To date, there is no cure for any single neurodegenerative disease, where diagnosis usually leads to debilitating symptoms and ultimately death, due in part to the lack of complete knowledge of the aetiological factors involved and a limited understanding of their pathological progression. While degenerative mechanisms are not yet fully elucidated, some common mechanisms leading to neurodegeneration have been identified, such as protein aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and impairments in autophagy.

Accumulating evidence indicating that intestinal microbiota influences brain function and behaviour across the lifespan has sparked interest in the role the gut microbiome plays in neurodegenerative disease. The gut microbiota of individuals with neurodegenerative disease differs from healthy people, suggesting a connection between the brain pathology and the gut microbiota. The microbiota-gut-brain axis is a bidirectional communication pathway where gut microbes signal to the brain and the brain signals to the gut. The mechanisms of communication are not fully understood due to large interconnected complex networks but include immune, neural, endocrine, and metabolic pathways [16]. A growing body of evidence now points towards a role for the gut microbiota in age-related disorders including neurodegenerative disease; however, the level of involvement of the gut microbiota in the pathology is still under debate. Our knowledge about the implications of gut microbiota in the pathogenesis of these diseases, as well as the number of therapeutic interventions targeting the gut microbiota for these diseases, are however increasing.

2 Neurodegenerative Diseases

Neurodegeneration is the generic term that describes the loss of neurons leading to a progressive dysfunction of the central nervous system. Neurodegenerative diseases are usually of unknown origin, and the pathogenesis is considered to be driven by a combination of genetic and environmental factors (with the possible exception of

Table 1 Overview of neurodegenerative diseases

Disease	Estimated incidence and prevalence per 100,000 people	Origin	Clinical features	Brain region affected	Aggregating proteins involved	Location of aggregates
Alzheimer's disease	Incidence: 2300 Prevalence: 14,500 in the USA in 2011 [4]	10% genetic, 90% sporadic [3]	Dementia	Hippocampus, cerebral cortex	Aβ, tau	Cytoplasmic, extracellular
Parkinson's disease	Incidence: 5–346 Prevalence: 65–12,500 in Europe in 2005 [6]	5–15% genetic and 85–95% sporadic [5]	Motor disorder	Substantia nigra	α-Synuclein	Cytoplasmic
Huntington's disease	Incidence: 0.4 in Europe in 2005 [7] Prevalence: 10.6–13.7 in Western populations in 2017 [8]	100% genetic	Motor, cognitive, and psychiatric disorder	Striatum, cerebral cortex	Huntingtin	Nuclear
Amyotrophic lateral sclerosis	Incidence: 2.5 Prevalence: 4–6 worldwide in 2012 [9]	10% genetic, 90% sporadic	Motor disorder	Motor cortex, brainstem	Superoxide dismutase, TPD-43	Cytoplasmic
Multiple sclerosis	Incidence: 1–10 in Europe [10] Prevalence: 50–300 worldwide in 2013 [13]	A combination of genetic and environmental interactions [11]	Autoimmune disease	White matter	Basson [12]	Cytoplasmic

Huntington's disease—HD—which is inherited in an autosomal dominant manner).[1] The knowledge around these conditions has increased notably in recent decades thanks to improvements in neuronal imaging and molecular techniques. However, this knowledge varies greatly amongst diseases, and Alzheimer's disease (AD) and Parkinson's disease (PD) are by far the most studied neurodegenerative diseases to date. A brief description of the most common and studied neurodegenerative diseases is given below as they will be mentioned throughout this chapter.

AD is the most common neurodegenerative disease affecting at least 43.8 million people worldwide [17], a number that is growing year after year and expected to double by 2050 [18]. AD is the most common diagnosis of dementia. The main neuropathological hallmarks of AD are the accumulation of extracellular amyloid-beta (Aβ) plaques and intraneuronal deposits of tau protein, a microtubule-associated protein, which constitutes the primary component of neurofibrillary tangles [19]. These pathological features lead to neuronal cell death in the hippocampus and the cerebral cortex and a decline in memory, thinking, and language abilities.

PD is the second most common neurodegenerative disease, and more than six million individuals worldwide were living with PD in 2016 [20]. It is characterised by a slow and progressive degeneration of dopaminergic neurons in the substantia nigra. This neuronal decay in the nigrostriatal pathway generates motor (bradykinesia, rigidity, resting tremor, and postural instability) and non-motor symptoms (constipation, anosmia, and sleep disturbances amongst others). In addition to neuronal loss, PD is also characterised by the presence of intraneuronal protein inclusions of α-synuclein, called Lewy bodies [21]. α-Synuclein is a small protein, mostly present in the presynaptic terminals of neurons, and its function, although not fully understood, is associated with synaptic function modulation and vesicle trafficking [22].

HD is a neurodegenerative disease caused by an inherited autosomal dominant CAG trinucleotide repeat in the huntingtin gene that causes neuronal dysfunction [8]. Hence, unlike other neurodegenerative diseases, HD pathogenesis is triggered by a genetic mutation. This neurodegeneration causes a wide spectrum of movement, cognitive, and psychiatric symptoms that appear in the first decades of adult life [8].

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease and affects motor neurons and causes muscular atrophy and weakness leading to difficulties in speaking and breathing and ultimately death [23]. In ALS, neurodegeneration and neuronal cell death are associated with excess synaptic glutamate and mitochondrial alterations [24]. A blockade of the neurotransmitter γ-aminobutyric acid (GABA) receptor in ALS causes muscle hyperexcitability and a moderate loss of motor neurons [25]. Thus, distortions in the fine balance between the excitatory glutamate activity and inhibitory GABA activity can severely

[1] Autosomal dominant inheritance pattern refers to how a mutation is inherited. In autosomal dominant inheritance, the mutation gene is located in a non-sex chromosome, and only one copy of the mutated gene is needed to be affected.

compromise motor neuron viability. Significant particularities of ALS versus other neurodegenerative diseases include a lower age of onset, fast decay of motor neurons, and quick mortality rate [26].

Multiple sclerosis (MS) is a neurodegenerative and inflammatory autoimmune disease where T cells in the immune system react against oligodendrocytes in the CNS, resulting in neuroinflammation, demyelination, and axonal loss [27]. The consequences of demyelination depend on the area affected but include ataxia, loss of coordination, visual and sensory impairment, and fatigue. The autoimmune profile of MS makes it different from the other neurodegenerative diseases as it is characterised by an earlier onset and episodic manifestations.

The conditions mentioned above do not represent a complete list of neurodegenerative diseases characterised thus far but represent the conditions where the role of the gut microbiome has been mostly investigated. There is a plethora of proteinopathies described in the literature that include infectious acquired neurodegeneration (such as that seen in prion-like disease, transmissible spongiform encephalopathies, or Creutzfeldt-Jakob disease) and conditions with mixed clinicopathological features such as dementia with Lewy bodies.

Although each neurodegenerative disease has a clearly defined set of diagnostic symptoms, most patients present with mixed clinical symptomatology, hampering an accurate diagnosis that in most cases cannot be confirmed until post-mortem. The rising complexity of neuropathological findings demands that all aspects of the clinical picture are analysed and not limited to the cardinal symptoms. Secondary symptomatology, including gastrointestinal, cognitive, and psychiatric manifestations, are increasingly being considered as a prodromal diagnostic tool for neurodegenerative disease, especially given that they can significantly impact quality of life. For example, symptoms of gastrointestinal dysfunction such as constipation are a common symptom of the prodromal phase in PD and can arise several years before any motor function deficits.

Hence, it is becoming increasingly evident that not only do disease-specific brain-related symptoms need to be considered. Gastrointestinal microbes were initially examined for GI-related conditions such as Crohn's disease and irritable bowel syndrome but are now under serious consideration in the field of brain neuropathies.

3 Gut Microbiota

The human microbiota is an entity that includes trillions of microorganisms (bacteria, viruses, fungi, phages, yeasts, archaea) that live in and on our bodies [28]. The gut microbiota specifically consists of a broad community of bacterial species that live in symbiosis in the human gastrointestinal tract and is essential for the digestion of non-digestible substrates in the host, such as dietary fibres [29]. The gut microbiota is also involved in many other functions including host metabolism, immune system regulation, and neuronal development.

The technological advancement of genetic sequencing techniques lately has dramatically improved our knowledge of the gut microbiota composition and abundance; it is estimated that our gastrointestinal tracts are populated with more than 500–1000 different bacterial species [30]. The human gut microbiota is mostly composed of bacterial strains belonging to the phyla[2] *Firmicutes* and *Bacteroidetes*, but other minority phyla that are commonly found include *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* [31]. The gut microbiota is a dynamic entity that experiences many shifts during the host lifespan and can be modulated by many external factors such as lifestyle choices and environmental inputs [32]. However, each individual harbours radically different microbial compositions, even in conserved taxa, and our knowledge about what regulates that variability is limited. For this reason, what constitutes the best microbiome composition is unknown.

Although microbial community composition in the gut has a great inter-individual variability, the maintenance or disruption of the host gut homeostasis, per individual, is key in health and disease. The overall composition ratios of gut microbiota in any one individual are very well conserved once adulthood is reached. In fact, changes in the microbiome and the subsequent relationship with biological systems such as the immune, endocrine, and central nervous system correlate with a broad range of diseases. In particular, the relative abundance between the two major phyla, expressed as the *Firmicutes*/*Bacteroidetes* ratio, has been linked with many pathological conditions [33], and it is currently used as an estimation of gut microbiota alterations. In the context of neurodegenerative diseases, intestinal microbiota dysbiosis[3] seems to contribute to neurodegeneration [35].

The implication of the gut microbiota in disease has sparked interest in the scientific community that foresees gut microbiota modulation as a potential target for therapeutic prevention and intervention. Many therapeutic interventions focused on the enhancement of beneficial bacteria have been described, such as the oral administration of probiotics, prebiotics, or faecal microbiota transplantation (FMT). In probiotic administration, live bacteria and/or yeasts, thought to be beneficial to health, are ingested, whereas prebiotic administration consists of the ingestion of non-digestible fibres that promote the growth of beneficial bacteria. FMT is the transplantation of gut microbiota from a donor individual into the GI tract of a recipient individual. In animal models, FMT has been used to investigate the pathogenic mechanisms of neurodegenerative diseases by transplanting the gut microbiota of healthy donors into a diseased recipient, or vice versa. These approaches are under investigation for neurodegenerative diseases and will be described later in this chapter.

[2] In taxonomy, living organisms are classified into eight ranks ranging from more general to more specific characteristics (domain, kingdom, phylum, class, order, family, genus, and species).

[3] Dysbiosis is an ambiguous term frequently used to describe disruptions of the gut microbial populations, and it is commonly associated to disease [34].

3.1 Gut Microbiota and Ageing

Ageing is an inevitable and progressive deterioration of physiological functions of the host that correlate with increased risk of disease and death. Ageing comes with modifications in life habits (such as diet or exercise) and physiological changes. The ageing process brings changes in gut physiology, as well as gut microbial composition and function [36]. The process of ageing has been classified as a sensitive period for gut microbiota, where it is susceptible to environmental triggers and intrinsic factors in the host [37]. However, the relationship between ageing and gut microbiota is thought to be bilateral, as the gut microbiota can also contribute to normal ageing. Ageing-associated gut microbiota changes result in increased gut permeability, modifications in the production of gut microbiota-derived metabolites, and alterations in the host immune system [38]. Age-associated shifts in the gut microbiota are linked to increased susceptibility to many diseases, including neurodegenerative diseases [39, 40].

The composition of the gut microbiota is markedly different between young and elderly populations [41–43] the latter being characterised by a lower microbial diversity [44, 45]. For instance, in some cohort studies, elderly populations had a reduced *Firmicutes*/*Bacteroidetes* ratio [46, 47], but not in others [48]. Also, a reduction in beneficial commensal bacteria such as *Bifidobacterium* and *Lactobacillus* and an increase in harmful bacteria such as *Enterobacteriaceae* are reported in aged individuals [49]. These microbial changes are linked to changes in physiology attributed to ageing but also to lifestyle changes such as modifications in diet, reduction of physical activity, and an increase in medications [46]. In ageing populations, a lower microbial diversity correlated with diseased conditions [46]. For example, loss of diversity in the core microbiota[4] groups is associated with increased frailty and reduced cognitive performance [50]. Although the mechanisms linking gut microbiota and brain are not fully understood, it is clear that microbial dysbiosis in the gut is associated with a higher risk of brain dysfunction.

4 The Microbiota-Gut-Brain Axis

The concept of a microbiota-gut-brain axis is relatively new but is increasingly accepted due to the mounting evidence that the gut microbiota can regulate brain-specific processes such as host behaviour [37]. The microbiota-gut-brain axis is comprised of bidirectional complex communication networks between the brain and the gastrointestinal tract. This bidirectional communication between the two organs involves many signalling pathways such as the enteric nervous system (ENS), the hypothalamic-pituitary-adrenal axis, the immune and endocrine systems, as well as the gut microbiota and its metabolites [16, 51]. Despite interest in and knowledge of

[4]The core microbiota refers to the taxa that are present in the vast majority of the subjects [41].

the microbiota-gut-brain axis increasing daily, there is still a lack of full understanding of the underlying mechanisms involved in these networks.

The relevance of the gut-brain axis in neurodegenerative diseases became evident 20 years ago when Dr. Braak and colleagues proposed an intriguing hypothesis that PD spread from the gut to the brain as a result of an infection [52]. They presented evidence of Lewy bodies outside the nigrostriatal pathway, in locations such as the olfactory bulb, the ENS, and the vagus nerve. According to Braak and colleagues, the first inclusions of α-synuclein occur in the vagus nerve and olfactory bulbs and then the pathology spreads in an ascending manner to the brainstem and forebrain [52]. Interestingly, the vagus nerve is one of the best characterised communication pathways between the brain and the gut [53]. Animal models were then developed to assess the gut-to-brain spread hypothesis. Now we know that α-synuclein can spread in a prion-like manner both in vitro and in vivo [54]. Moreover, the transport of different forms of α-synuclein from the gut to the brain through the vagus nerve has been reported in rats [55]. However in a recent animal study, although the expected brain-to-gut spread of α-synuclein could not be confirmed, alterations in the ENS and the gut microbiome were apparent [56]. Interestingly, gut-seeded α-synuclein fibrils promoted gut dysfunction and brain pathology in aged mice but not in young mice [57]. Despite the point of origin of PD in the body still being a matter of debate, these investigations have highlighted the importance of the role that the gut-brain axis plays in PD.

Most neurodegenerative diseases were initially viewed as neuronal brain-exclusive diseases, but recent findings have challenged this idea and neurodegenerative diseases are now viewed as a multisystemic disease. Although ageing, genetics, and the environmental are important risk factors for neurodegeneration, as we will see later on, the involvement of the gut microbiome through the bidirectional gut-brain axis cannot be diminished. As a result, much research now focuses on the potential implications of the microbiome in these diseases.

5 Towards Neurodegeneration

For decades, neuroscientists were focused on the specifics of the neuronal decay in each neurodegenerative disease. However, it is now more evident that there are clinical, cellular, and molecular differences that neurodegenerative diseases share, which contribute to the development of neurodegeneration. Furthermore, they share common pathogenic pathways that lead to neurodegeneration. Below, we discuss the main factors contributing to neurodegenerative disease (see Fig. 1).

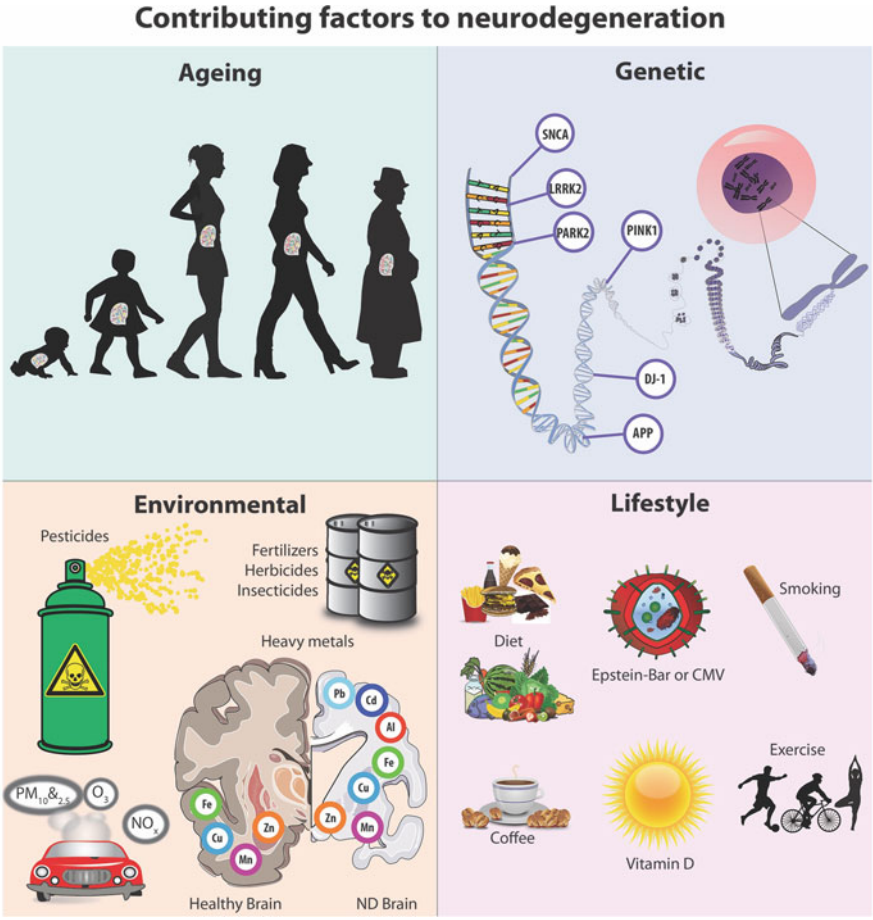

Fig. 1 Known factors that contribute to neurodegenerative disease. The aetiology of neurodegenerative diseases is mostly unknown, but several factors such as ageing, genetics, environmental, and lifestyle choices contribute to the pathogenesis of neurodegenerative diseases. SNCA, synuclein alpha; LRRK2, leucine-rich repeat kinase 2; PARK2, Parkinson disease-2; PINK1, PTEN [phosphatase and tensin homolog]-induced kinase 1; DJ-1, protein deglycase; APP, β-amyloid precursor protein; PM (particulate matter) 10 (<10 μm) 2.5 (<2.5 μm); O_3 (ozone/trioxygen); NO_X, nitrogen oxides; Fe, iron; Cu, copper; Zn, zinc; Mn, manganese; Al, aluminium; Cd, cadmium; Pb, lead; CMV, cytomegalovirus; ND, neurodegenerative disease

5.1 Factors that Contribute to the Development of Neurodegeneration

5.1.1 Ageing

The growth of an ageing population worldwide is increasing rapidly, and with it, the incidence of neurodegenerative diseases. From a cellular and molecular perspective,

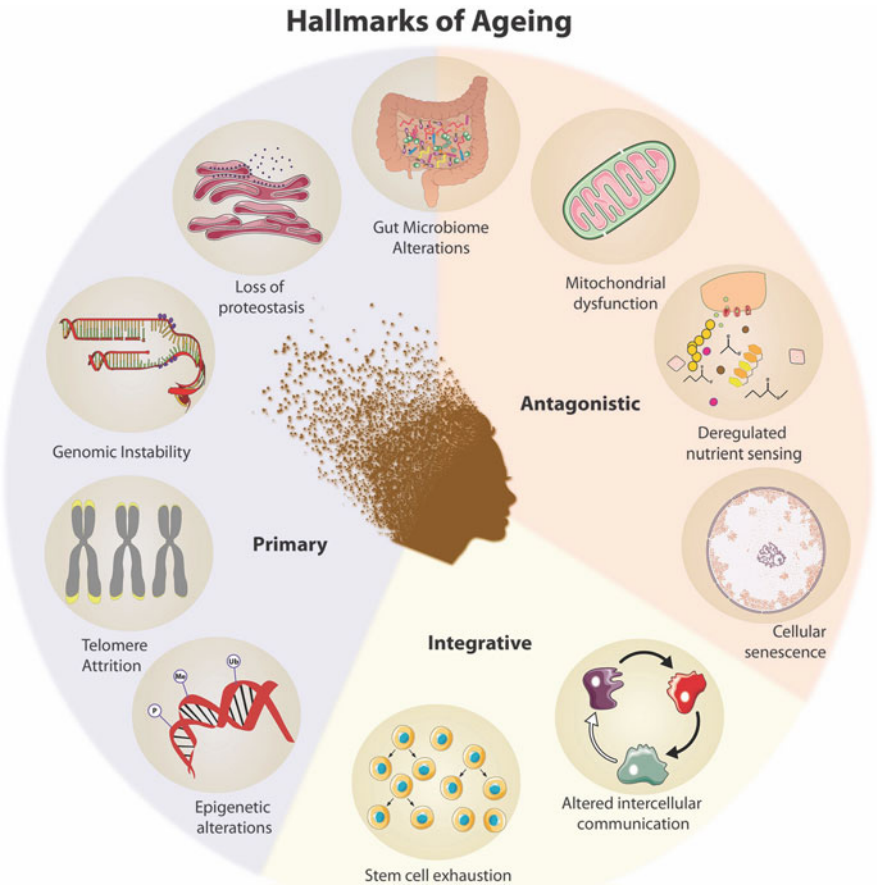

Fig. 2 The main hallmarks of ageing. From a cellular and molecular perspective, the nine hallmarks of ageing have been identified and grouped into primary, antagonistic, or integrative hallmarks

the nine hallmarks of ageing have been identified and grouped into primary, antagonistic, or integrative hallmarks (see Fig. 2) [58]. The primary hallmarks of ageing include genomic instability, epigenetic alterations, telomere attrition, and loss of proteostasis,[5] which are considered to be unequivocally negative processes. The antagonistic hallmarks—mitochondrial dysfunction, cellular senescence, and deregulated nutrient sensing—unlike the primary hallmarks, can have beneficial or deleterious effects depending on their intensity. The integrative hallmarks—stem cell exhaustion and altered intercellular communication—arise as the culprit of the accumulative damage induced by primary and antagonistic hallmarks. These central

[5] Regulatory processes that involve synthesis or degradation of proteins to maintain cell health.

biological mechanisms of ageing and their relationship with neurodegeneration have been reviewed elsewhere [59].

The absence of disease-free brains in the oldest population suggests that brain ageing and neurodegeneration are a continuum rather than a simplistic cause-effect relationship [60]. Thus, not only ageing but congenital predisposition and environmental factors will determine the lesions that will lead to specific diseases.

5.1.2 Congenital Factors

Genetic studies have shown that genetic predisposition plays an important role in the development of neurodegenerative disorders such as AD or PD, especially in young adult onset cases where specific mutations have been identified [61, 62]. In early onset familial AD, mutations in three genes (amyloid precursor protein (APP), presenilin-1, and presenilin-2) involved in the Aβ plaque formation have been identified as inherited in an autosomal dominant pattern [61]. In the familial forms of PD, genes (*SNCA*, *LRRK2*, *PARK2*, *PINK1*, *DJ-1*, and *ATP13A2*) have been identified to be hereditable monogenic PD [63]. In contrast, HD is an exception to neurodegenerative diseases, as the genetic component is needed for the development of the disease.

However, most chronic neurodegenerative diseases are considered to have a multifactorial aetiology since most of the cases are sporadic and cannot be attributed solely to genetic factors.

5.1.3 Environmental Factors

There is mounting evidence that environmental factors play a crucial role in the development of neurodegenerative diseases, in particular in AD and PD. Pesticides, herbicides, fertilisers, and particulate matter (PM), ozone (O_3), nitric oxide, and heavy metals have been demonstrated as having an increased risk of developing AD [64, 65], PD [66, 67], and ALS [68] (see Fig. 1). Pesticides and heavy metals can be neurotoxic leading ultimately to neurodegeneration [69]. Interestingly, some of these environmental factors can directly affect gut microbiota. It is believed that a complex combination of genetic and environmental interactions is key for disease pathogenesis and that the microbiome is a participant in this intricate network of factors. However, how these environmental factors interact is not fully understood, and more investigations on these interactions are needed as they could elucidate mechanisms of pathogenesis and improve prevention and personalised therapy for these diseases [70].

5.1.4 Lifestyle

Lifestyle choices and experiences have also been linked to the development of these diseases. For example, sport-related traumatic brain injury has been reported to increase the risk of developing both AD and PD [71, 72], whereas coffee consumption, smoking [73], and vigorous exercise [74] correlated with a decreased risk for PD and the Mediterranean diet for AD [75]. Lifestyle risk factors for MS include smoking, vitamin D deficiency or low sun exposure, and infections of Epstein-Bar virus or cytomegalovirus [76]. These lifestyle factors can impact gut microbiota, once more highlighting the complexity of factors and systems involved in neurodegeneration diseases.

5.2 Common Pathways to Neurodegeneration

Although each neurodegenerative disease has its own singular pathogenic mechanisms, some commonalities arise in the pathways leading to neurodegeneration.

5.2.1 Protein Misfolding

The most common neurodegenerative disorders are proteinopathies, characterised by the misfolding, aggregation, and accumulation of disease-specific proteins. These proteins change their conformation resulting in a loss of their biological function and can become toxic. AD, characterised by the formation of Aβ deposits as amyloid plaques, as well as neuronal tau inclusions, is probably the most salient proteinopathy, although many others exist such as PD, HD, frontotemporal dementia, and spinocerebellar ataxia type 1. The molecular mechanisms, causing a normal protein with a physiological function to transform into an abnormal conformation, are not well understood [77].

Protein homeostasis is a tightly regulated process essential for cellular integrity. Misfolded or aggregated proteins are quickly targeted by molecular chaperones that repair or degrade faulty proteins to maintain cellular homeostasis [78]. Molecular chaperones use the ubiquitin proteasome system and autophagy pathways to degrade these proteins [79]. However, these systems are altered in many neurodegenerative diseases, facilitating the accumulation of these aberrant proteins. Moreover, cellular ageing, proteotoxic stress, or genetic mutations can interfere with this process, resulting in proteins that escape the cell's quality control system and aggregate into non-native structures [78]. Consequently, although misfolded proteins in neurodegenerative diseases (α-synuclein, Aβ, huntingtin) have very different biological function and location, they share a β-sheet-rich tertiary structure in their pathological form, which facilitates their aggregation into oligomeric fibrillar formations [80].

Thus, despite having differential molecular agents implicated, neurodegenerative diseases share many common altered hallmarks that explain this accumulation of aberrant proteins.

5.2.2 Glial Cells and Neuroinflammation

The brain is not only populated by neurons, in fact, it's estimated that glial cells are at least as abundant as neurons [81]. Neurodegenerative diseases are multicellular in nature, and the implication of both neuronal and non-neuronal populations is now being investigated. This shift was based on extensive research data, showing first the presence of neuroinflammation in neurodegenerative disease, and second, the involvement of glial cells in disease progression. There is compelling evidence that neurodegenerative diseases such as AD, PD, and MS, are strongly associated with immune activation and neuroinflammation [82, 83].

Most neurodegenerative diseases display increased levels of neuroinflammation, which is the inflammatory response in the brain. This permeabilisation leads to lymphocyte infiltration. Neuroinflammation involves the activation of microglia and astrocytes, which secrete inflammatory molecules such as cytokines and chemokines. Evidence from both individuals and animal models reports that there is a recruitment of glial cells into the afflicted areas. For example, activated microglia and/or astrocytes are found in the substantia nigra of PD patients [84, 85] and AD patients, respectively [86]. Not only are innate immune cells found in neurodegenerative processes, cytotoxic T lymphocytes—major cell components of the adaptive immune system—were also reported to be higher in blood and in the affected PD brain regions, than in healthy subjects [87, 88]. The selective location of these T cells indicates an infiltration to the brain parenchyma, suggesting a disruption of the blood-brain barrier (BBB). Altered permeability in the BBB is a common pathological feature in many neurodegenerative diseases [89, 90].

At a molecular level, neuroinflammation has also been confirmed, where increased levels of pro-inflammatory molecules such as tumour necrosis factor α (TNF-α), interleukin 1β (IL-1β), and interferon γ (IFN-γ) were present in the serum and cerebrospinal fluid of PD patients and in the nigrostriatal pathway at *post-mortem* analysis [91]. Thus, although the identification of neuroinflammation during the progression of neurodegeneration is largely understood, these data do not confirm the involvement of neuroinflammation in the degenerative process. However, genetic and epidemiological studies have shown that polymorphisms in neuroinflammation-related genes increase the susceptibility for PD [91] and mutations in APOE and TREM2 genes, mainly expressed in glial cells, increase the risk for AD [92]. Further, genes linked to major histocompatibility complex (MHC) class II have been found to be a risk factor for MS [93].

This evidence together suggests that neuroinflammation is linked to the neurodegenerative process, playing a crucial role in disease progression. First, protein aggregates cause a direct inflammatory reaction that eventually leads to neuronal cell death. Immune responses are a double-edged sword however, with beneficial or

deleterious consequences depending on the specific situation. Furthermore, these cellular and molecular changes seen in patients have been observed in animal models too.

Independent of the origin of neuroinflammation, immunotherapies targeting the neuroinflammation in neurodegenerative diseases could help halt or modify the course of disease. Many immune-based therapeutic interventions are under investigation, including targeting the clearance of protein aggregates, with the inhibition of inflammation and apoptosis amongst other mechanisms of action [94].

5.2.3 Mitochondrial Dysfunction and ROS Generation

Neurons consume high amounts of energy to perform [95]; hence, they rely on mitochondria to fulfil these high metabolic demands. Mitochondria not only produce high quantities of ATP, but they also regulate calcium concentration and generate reactive oxygen species (ROS) from the respiratory chain [96].

Misfolded proteins can negatively affect mitochondria by several mechanisms including direct damage to mitochondrial DNA, trafficking impairment, or promoting mitochondria-dependent cell death pathways [97]. This mitochondrial dysfunction is well known in AD, where Aβ and tau proteins disrupt mitochondrial DNA maintenance, protein import, electron transport chain activity, and reduction-oxidation (redox) balance [97]. Similarly, α-synuclein accumulation in mitochondria reduced mitochondrial complex I activity and increased free radical production in dopaminergic neurons [98]. Mitochondria in motor neurons of ALS patients have an altered structure and appear swollen and vacuolated under histological analysis [99]. *Post-mortem* analysis of ALS brains showed alterations in respiratory chain complexes within mitochondria [100, 101].

Gene mutations are another factor linked to mitochondrial dysfunction. In PD, mutations in PINK1, Parkin, and DJ-1 are closely associated with mitochondrial dysfunction [102, 103]. Parkin and PINK-1 are known regulators of mitophagy, the autophagic process responsible for clearing the cell of defective mitochondria [104, 105].

If mitochondrial dysfunction in neurodegenerative diseases is a cause or a consequence, it's still under consideration, but it seems plausible that a reciprocal toxic cycle exists. Mitochondria are the main source of ROS production, including superoxide (O_2^-), hydroxyl (HO), and hydrogen peroxide (H_2O_2) radicals, which are a by-product of oxidative phosphorylation in cellular respiration. In neurodegeneration, the implication of oxidative damage as a pathogenic factor is well known, and as a result, has often been a target of potential therapeutic treatments; however, clinical trials assessing the benefits of antioxidants in neurodegenerative diseases have been generally negative [106].

5.2.4 Protein Clearance Systems: UPS and Lysosome Dysfunction

The ubiquitin-proteasome system (UPS) is a crucial protein degradation process in cells; briefly, proteins tagged with ubiquitin are targeted for proteasome degradation. Proteasomal turnover is particularly challenging for neurons due to their distinctive morphology (long axons and complex dendritic ramifications) [107]. Lysosomes—the organelle responsible for clearance of cellular debris—become dysfunctional in the pathogenesis of neurodegenerative disease. Lysosomes may be one of the key mechanisms underlying the accumulation of aberrant proteins in neuronal cells.

Interestingly, α-synuclein is degraded via UPS and autophagy-lysosome pathways [108, 109], leading to UPS regulation and lysosomal modification as potential methods of ND therapies.

5.2.5 Microbial Metabolites

Gut microbiota alterations have been observed in neurodegenerative diseases. Short-chain fatty acids (SCFAs)—which include acetate, propionate, and butyrate—are metabolites produced by bacterial fermentation of dietary fibres in the colon and are thought to be key mediators in the gut microbiota-brain axis crosstalk. However, most of the mechanisms by which SCFAs exert these effects remain yet unknown and need to be investigated further.

Tryptophan metabolism is one of the most important signalling pathways of the gut microbiota. Tryptophan is an essential amino acid which serves as a precursor to biosynthetic compounds, such as serotonin, melatonin, and nicotinamide adenine dinucleotide (NAD^+). The tryptophan-kynurenine metabolic pathway degrades tryptophan into several metabolites with inflammatory, oxidative, and neuronal modulatory properties [110]. Moreover, kynurenine enzymes further influence inflammatory processes [111]. Thus, this complex balance between neuroprotective and neurotoxic agents is crucial for the brain, and disturbances in the gut microbiota or other relevant processes such as inflammation could destabilise this equilibrium. In fact, in a systematic review, neurotoxic kynurenines were invariably increased in all major neurodegenerative diseases, while neuromodulatory kynurenines were decreased in AD, PD, and HD [110].

6 The Role of Gut Microbiota in Neurodegenerative Disorders

Through the microbiota-gut-brain axis, gut microbiota can modulate brain function and behaviour across the lifespan, both in health and disease [37]. However, the microbiota-gut-brain axis is bidirectional, as neurodegenerative brain dysfunction can also impact on the gut microbiota [112]. It encompasses a tentative relationship

that is somewhat sensitive to neuronal cell death and generalised inflammation. Furthermore, as mentioned earlier, neurodegenerative disorders are most frequent in aged populations, and ageing directly modifies the gut microbiota. Consequently, the gut microbiota composition of patients suffering from neurodegenerative diseases differs significantly from healthy subjects. In most cases, the relationship between the gut microbiota and neurodegeneration has been reported recently, but if dysbiosis is the cause or the consequence of the pathogenesis is still being investigated.

The gut microbiota and its metabolites interact with many of the pathways leading to neurodegeneration. Thus, it comes as no surprise that many studies have linked microbial dysbiosis to the pathology of neurodegenerative diseases [113, 114]. For instance, reduced diversity of gut microbiota during ageing and neuroinflammation are two common features of gut dysbiosis and neurodegeneration. Gut microbiota are constantly regulating microglial activation [115], and this could have great implications in neurodegeneration. These findings suggest that this process could be manipulated by microbiome-targeted strategies (see Fig. 3). It has been suggested that SCFA-producing bacteria could modulate immune activation in the brain [35]. Similarly, the porousness of the BBB could also be targeted via gut microbiome, as BBB permeability depends on microbiota composition [116].

Next we will summarise the main gut microbiota alterations observed in neurodegenerative diseases (see Table 2).

6.1 PD and Microbiome

Evidence for a role of the microbiome in PD comes from both animal and human studies. Regarding mouse models, PD pathophysiology is greatly reduced in the germ-free mouse—mice lacking any gut microbes—models of induced PD, and this effect can be reversed with oral administration of bacterial metabolites or an FMT [154]. Accordingly, antibiotic treatment ameliorated, while microbial recolonisation promoted, pathophysiology in mice overexpressing α-synuclein. Recently, a preclinical study reported that a gut bacterial amyloid promoted α-synuclein aggregation and motor impairment in mice [155]. These investigations suggest that gut microbiota is required for motor deficits, microglia activation, and α-synuclein pathology, at least in mice.

Gastrointestinal symptoms such as constipation are known to appear in PD patients well before the onset of the motor symptoms [156]. These gastrointestinal comorbidities—constipation, diarrhoea, and microbial dysbiosis—are common in most neurodegenerative diseases, which implicate the gut microbiome in neurodegenerative processes. Interestingly, the full removal of the vagus nerve—a surgical procedure called vagotomy—reduced the risk of developing PD in a clinical cohort [157].

Recently, the gut microbiota of PD patients has been investigated and compared to healthy controls (HCs) in a growing number of studies. Gut microbiota in PD

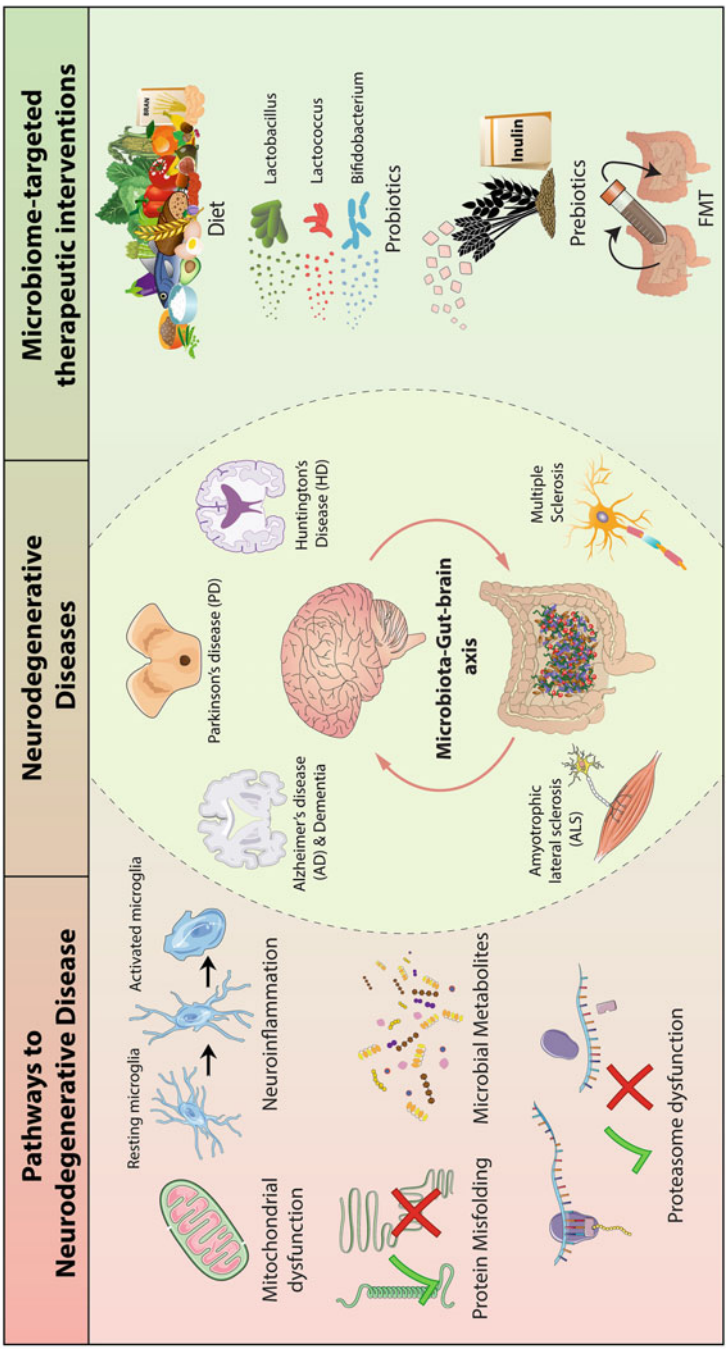

Fig. 3 Microbiota-targeted therapeutic interventions for neurodegenerative disease. The microbiota-gut-brain axis is linked to neurodegenerative diseases and interacts with many factors involved with neurodegeneration. Thus, new therapeutic approaches targeted to the gut microbiota are emerging for neurodegenerative diseases. ALS, amyotrophic lateral sclerosis; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; FMT: faecal microbiota transplantation

Table 2 Microbiota alterations in individuals with neurodegenerative disease versus healthy controls (HCs)

Type of study	Participants	Results	Conclusions
Alzheimer's disease			
Cross-sectional, observational [117]	Individuals with AD ($n = 24$), with other dementias ($n = 33$), or no dementia ($n = 51$)	Microbiome diversity differs between elders with AD and those with no dementia or other types of dementia. Individuals with AD had increased proportions of *Bacteroides* spp., *Alistipes* spp., *Odoribacter* spp., and *Barnesiella* spp. and decreased proportions of *Lachnoclostridium* spp. Individuals with other dementias had increased proportions of *Odoribacter* spp. and *Barnesiella* spp. and decreased proportions of *Eubacterium* spp., *Roseburia* spp., *Lachnoclostridium* spp., and *Collinsella* spp.	The gut microbiota composition differed in individuals with AD dementia in comparison to elders without dementia or with other dementia types
Cross-sectional, observational [118]	Individuals with AD ($n = 43$) and sex- and age-matched healthy controls (HCs) ($n = 43$)	Individuals with AD had decreased abundance of *Bacteroidetes*, *Verrucomicrobia*, *Negativicutes*, *Bacteroidia*, *Lachnospiraceae*, *Bacteroidaceae*, and *Veillonellaceae* and increased abundance of *Actinobacteria*, *Bacilli*, *Ruminococcaceae*, *Enterococcaceae*, and *Lactobacillaceae* compared with HCs	The gut microbiota composition and diversity of AD individuals were found altered compared with cognitively normal controls
Blind, cross-sectional, observational [119]	Cognitively impaired and amyloid-positive individuals ($n = 40$), cognitively impaired and amyloid-negative individuals ($n = 34$), and cognitively healthy and amyloid-negative individuals ($n = 10$)	Cognitively impaired amyloid-positive individuals had decreased abundance of *Bacteroides fragilis* and *Eubacterium rectale* and increased abundance of *Escherichia* and *Shigella*; significant upregulation of NLRP3,	Cognitively impaired individuals exhibited an increase in the abundance of pro-inflammatory gut microbial groups and a reduction in the abundance of anti-inflammatory microbial groups.

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		CXCL2, IL-6, and IL-1β, and downregulation of IL-10	Pro-inflammatory cytokines were also upregulated in these individuals
Blind, cross-sectional, observational [120]	Individuals with AD ($n = 25$) and sex- and age-matched HCs ($n = 25$)	Individuals with AD had reduced α-diversity and β-diversity and decreased abundance of *Firmicutes*. At a genus level, individuals with AD had increased abundance of *Alistipes*, *Bilophila*, *Blautia*, *Gemella*, and *Shigella* and reduced abundance of genus *Adlercreutzia* and *Bifidobacterium* compared with HCs	Individuals with AD had decreased microbial richness and diversity and a distinct microbial composition compared to control individuals
Parkinson's disease			
Cross-sectional, observational [121]	Individuals with PD ($n = 95$) and HCs ($n = 57$)	Individuals with PD had lower fungal DNA relative to bacterial DNA amongst PD patients. No fungi differed in abundance between groups nor were any associations with motor, cognitive, or gastrointestinal features	The gut mycobiome did not differ between individuals with PD and healthy individuals
Cross-sectional, observational [122]	Individuals with PD ($n = 197$) and age-matched HCs ($n = 103$)	No difference in α-diversity was observed between groups; α-diversity positively correlated with stool firmness. Individuals with PD had a higher abundance of *Christensenellaceae* and *Desulfovibrionaceae* at a family level and *Bifidobacterium*, *Collinsella*, *Bilophila*, and *Akkermansia* at a genus level. PD microbiota was enriched for pathways related to nucleic acid degradation and amino acid metabolism	Microbiota of PD individuals was characterised by reduced carbohydrate fermentation and butyrate synthesis capacity and increased production of harmful amino acid metabolites

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
Cross-sectional, observational [123]	Individuals with PD ($n = 9$) and HCs ($n = 13$)	No differences in α-diversity or β-diversity between groups. Individuals with PD had increased abundance of *Akkermansia*, and a trend towards increased *Bifidobacterium* and decreased *Prevotella* was observed	PD individuals have a specific gut microbiota composition that could be used as biomarkers
Cross-sectional, observational [124]	Individuals with PD and mild cognitive impairment ($n = 13$), individuals with PD and normal cognition ($n = 13$), and HCs ($n = 13$)	In individuals with PD and mild cognitive impairment, the families *Rikenellaceae* and *Ruminococcaceae* and the genera *Alistipes*, *Barnesiella*, *Butyricimonas*, and *Odoribacter* were in higher abundance compared with the other two groups. Genera *Blautia* and *Ruminococcus* were decreased in the PD mild cognitive impairment group compared with the PD normal cognition group. The abundance of genera *Butyricimonas*, *Barnesiella*, *Alistipes*, *Odoribacter*, and *Ruminococcus* negatively correlated with cognition ability	Microbiota of individuals with PD and mild cognitive impairment substantially differed from individuals with PD and normal cognition, indicating a correlation between microbial communities and cognition
Cross-sectional, longitudinal, observational [125]	Individuals with PD ($n = 64$) and sex- and age-matched HCs ($n = 64$), 2 years apart	β-diversity was reduced in PD individuals versus HCs. No differences were observed in the *Firmicutes*/*Bacteroidetes* ratio between groups, but *Prevotella*/*Bacteroides* was higher in HCs. Differences in abundances in *Bifidobacterium*, *Prevotella*, *Lactobacillus*, and *Roseburia* were seen in both groups. Progressed PD individuals were overrepresented in the *Firmicutes*-	Alterations in gut microbiota in individuals with PD persisted after 2 years

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		dominated enterotype. Prevotella was less abundant in PD individuals compared to controls and also appears less abundant in individuals with faster disease progression	
Cross-sectional, observational [126]	Individuals with sporadic PD ($n = 75$) and age-matched HCs ($n = 45$)	Individuals with PD had decreased abundances of *Tenericutes*, *Euryarchaeota*, and *Firmicutes* at a phylum level and *Lachnospiraceae* at a family level. *Rikenellaceae* and *Deferribacteraceae* were more abundant in individuals who had suffered from PD for more than 5 years. *Leptotrichia* (*Fusobacteria*) was increased in individuals with PD and tremor, whereas *Roseburia* (*Lachnospiraceae*) was more abundant in individuals with PD and without tremor	Alterations in microbiota seen in individuals with PD were closely related to PD clinical characteristics
Cross-sectional, observational [127]	Individuals with sporadic PD ($n = 10$) and age-matched HCs ($n = 10$)	In individuals with PD, the abundance of the family of *Bacteroides* and *Prevotellaceae* was decreased, while the abundance of *Ruminococcaceae*, *Verrucomicrobiaceae*, *Porphyromonadaceae*, and *Lachnospiraceae* NK4A was enriched in north-eastern Han Chinese individuals with PD	The microbiota alterations in Chinese individuals with PD showed some similarities and disparities to individuals with PD from another region
Cross-sectional, observational [128]	Individuals with PD ($n = 58$) and HCs ($n = 45$)	In individuals with PD, the genera *Clostridium IV*, *Aquabacterium*, *Holdemania*, *Sphingomonas*, *Clostridium XVIII*,	Alterations in microbiota seen in individuals with PD were closely related to PD clinical characteristics

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		Butyricicoccus, and *Anaerotruncus* were enriched in comparison to HCs. *Escherichia/Shigella* abundance was negatively associated with disease duration, and genus *Dorea* and *Phascolarctobacterium* were negatively associated with levodopa administration. *Butyricicoccus* and *Clostridium XIVb* were associated with cognitive impairment	
Cross-sectional, observational [129]	Individuals with PD ($n = 76$), individuals with idiopathic rapid eye movement sleep behaviour disorder ($n = 21$), and HCs ($n = 78$)	Individuals with PD had a differential abundance of *Anaerotruncus*, *Clostridium XIVb*, several *Bacteroidetes*, *Akkermansia*, and *Verrucomicrobiaceae* compared with HCs. Similar trends in these alterations were also observed in idiopathic rapid eye movement sleep behaviour disorder versus HCs for example, *Anaerotruncus* and several *Bacteroides* spp., correlated with nonmotor symptoms	Individuals with PD or its prodrome idiopathic rapid eye movement sleep behaviour disorder had differential abundances of gut microbial taxa in comparison with HCs
Cross-sectional, observational [130]	Individuals with PD ($n = 29$) and HCs ($n = 29$)	β-diversity analyses, but not α-diversity, differed between groups. Individuals with PD had higher abundance of *Lactobacillaceae*, *Barnesiellaceae*, and *Enterococcaceae* in comparison with HCs	Gut microbiota in PD individuals was characterised by a decrease in taxonomic diversity and significant differences in the bacterial community
Cross-sectional, observational [131]	Individuals with PD ($n = 24$) and HCs ($n = 14$)	Individuals with PD had decreased abundances of *Blautia*, *Faecalibacterium*, and *Ruminococcus* and increased abundances of	The unbalance in beneficial and harmful bacteria in individuals with PD may help explain PD pathogenesis

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		Escherichia-Shigella, *Streptococcus*, *Proteus*, and *Enterococcus* in comparison with HCs. Disease severity and PD duration negatively correlated with beneficial bacterial strains and positively correlated with pathobionts	
Cross-sectional, observational [132]	Individuals with PD ($n = 89$) and age-matched HCs ($n = 66$)	Individuals with PD had reduced α-diversity and abundance of *Dorea*, *Bacteroides*, *Prevotella*, *Faecalibacterium*, *Bacteroides massiliensis*, *Stoquefichus massiliensis*, *Bacteroides coprocola*, *Blautia glucerasea*, *Dorea longicatena*, *Bacteroides dorei*, *Bacteroides plebeus*, *Prevotella copri*, *Coprococcus eutactus*, and *Ruminococcus callidus* and increased abundance of *Christensenella*, *Catabacter*, *Lactobacillus*, *Oscillospira*, *Bifidobacterium*, *Christensenella minuta*, *Catabacter hongkongensis*, *Lactobacillus mucosae*, *Ruminococcus bromii*, and *Papillibacter cinnamivorans*	Gut microbiota in PD individuals was characterised by a decrease in taxonomic diversity and significant differences in the bacterial community
Cross-sectional, observational [133]	Individuals with PD ($n = 197$) and HCs ($n = 130$)	Individuals with PD had decreases in abundance of *Bifidobacterium*, *Lachnospiraceae*, and *Blautia* in comparison with HCs. The abundance of *Ruminococcaceae* significantly increased with length of PD symptoms in individuals with PD	PD individuals had an altered abundance of several taxa, and there were independent effects of PD medications on the microbiome

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
Cross-sectional, observational [134]	31 male individuals with PD ($n = 31$) and male age-matched HCs ($n = 28$)	Individuals with PD had increased *Verrucomicrobiaceae* (*Akkermansia muciniphila*) and unclassified *Firmicutes*, whereas *Prevotellaceae* (*Prevotella copri*) and *Erysipelotrichaceae* (*Eubacterium biforme*) were markedly lowered in PD individuals. The intake of either a MAO inhibitor, amantadine, or a dopamine agonist had no overall influence on taxa abundance or microbial functions	Perturbations in the gut microbiome composition of individuals with PD were observed
Cross-sectional, observational [135]	Individuals with PD ($n = 34$) and HCs ($n = 34$)	Faecal SCFA concentrations were significantly reduced in PD individuals compared to HCs. The bacterial phylum *Bacteroidetes* and the bacterial family *Prevotellaceae* were reduced, whereas *Enterobacteriaceae* were more abundant in faecal samples from PD individuals compared to matched controls	An altered microbiota with lower levels of SCFA-producing bacteria was associated with PD
Cross-sectional, observational [136]	Individuals with PD ($n = 38$) and HCs ($n = 34$)	Individuals with PD had increased abundance of *Bacteroidetes*, *Proteobacteria*, and *Verrucomicrobia*. At a genus level, PD individuals had lower abundances of butyrate-producing bacteria from the genera *Blautia*, *Coprococcus*, *Roseburia*, *Faecalibacterium*, and *Ralstonia* compared with HCs	Individuals with PD had a pro-inflammatory gut dysbiosis in comparison to healthy individuals
Randomised, cross-sectional,	Individuals with PD ($n = 52$) and HCs ($n = 36$)	In PD individuals, the abundance of hydrogen-producing bacteria was lower compared with	Intestinal permeability was increased in PD individuals, while the

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
observational [137]		HCs. In these individuals, there was a significant increase in *Lactobacillus* and decrease in *Clostridium coccoides* group, *Clostridium leptum* subgroup, and *Bacteroides fragilis* compared to HCs. Linear regression models revealed that the increased count of *L. gasseri* subgroup was associated with disease duration. In PD individuals, serum lipopolysaccharide (LPS)-binding protein levels were lower than healthy controls, while the levels of serum diamine oxidase remained unchanged in both groups	intestinal mucosal integrity was preserved
Case-controlled, observational [138]	Individuals with PD ($n = 72$) and HCs ($n = 72$)	Individuals with PD had a significant decrease in *Prevotellaceae* compared with control individuals. The abundance of *Enterobacteriaceae* was positively associated with the severity of motor symptoms	The intestinal microbiome was altered in PD and was related to motor phenotype
Huntington's disease			
Case-controlled, observational [139]	Individuals with HD ($n = 33$, 9 pre-manifest stage and 24 diagnosed HD) and sex- and age-matched HCs ($n = 33$)	Increased α-diversity, β-diversity, and altered relative abundances of several taxa compared to those in HCs. *Intestinimonas* and *Bilophila* correlated with concentrations of pro-inflammatory cytokines in HD patients. HD patients had higher abundances of *Intestinimonas*, *Bilophila*, *Lactobacillus*, *Oscillibacter*, *Gemmiger*, and *Dialister* at the genus	Gut microbiota of HD patients correlated with HD clinical characteristics and cytokine levels

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		level and lower abundance of *Clostridium XVIII* at the genus level	
Case-controlled, observational [140]	Individuals with HD ($n = 42$, 23 pre-manifest stage and 19 diagnosed HD) and sex- and age-matched HCs ($n = 36$)	Reduced α-diversity, β-diversity, and altered relative abundances of several taxa compared to those in HCs. Lower abundances of *Firmicutes*, *Lachnospiraceae*, and *Akkermansiaceae* in male HD patients	HD patients had increased abundances of gut bacterial families linked to pro-inflammatory processes
Multiple sclerosis			
Case-controlled, observational [141]	Individuals with relapsing-remitting MS ($n = 19$) and sex- and age-matched HCs ($n = 17$)	MS patients with high disease activity and increased intestinal TH17 cell frequency showed a higher Firmicutes/*Bacteroidetes* ratio, increased relative abundance of *Streptococcus*, and decreased *Prevotella* strains compared to HCs and MS patients with no disease activity. The relative abundance of *Prevotella* strains was inversely related to the intestinal TH17 cell frequency	Specific microbiota modifications were associated with excessive TH17 cell expansion in the human intestine in individuals with MS
Case-controlled, cross-sectional, observational [142]	Individuals with relapsing-remitting MS who had not received treatment for at least 3 months before sample collection ($n = 71$) and HCs ($n = 70$)	No differences in α-diversity or β-diversity between groups. Individuals with MS had increases in *Acinetobacter* and *Akkermansia* and decreases in *Parabacteroides*. MS individuals showed an impaired ability to differentiate or expand CD25-positive, FoxP3-positive regulatory T cell populations	Specific bacteria were associated with MS, and these bacteria regulated T lymphocyte-mediated adaptive immune responses and contributed to the pro-inflammatory environment of MS
Case-controlled, cross-sectional,	Individuals with relapsing-remitting MS ($n = 31$) and sex- and	β-diversity differed as a function of relapse status. Individuals with MS had	Perturbations in the gut microbiome

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
observational [143]	age-matched HCs ($n = 50$)	increases in abundance of *Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia*, and *Dorea* and lower abundance of *Parabacteroides* and *Adlercreutzia* compared to HC	composition were observed in relapsed-remitting MS
Case-controlled, cross-sectional, observational [144]	Children with MS ($n = 18$, within 2 years of relapsing-remitting MS onset) and age-matched HCs ($n = 17$)	β-diversity significantly differed by immunomodulatory drug exposure. Children with MS had increased relative abundance of *Bilophila*, *Desulfovibrio*, and *Christensenellaceae* and decreased relative abundance of *Lachnospiraceae* and *Ruminococcaceae* in children with relapsing-remitting MS compared with HC	Perturbations in the gut microbiome composition were observed in paediatric MS onset
Case-controlled, cross-sectional, observational [145]	Individuals with relapsing-remitting MS ($n = 60$) and HCs ($n = 43$)	MS individuals have increases in *Methanobrevibacter* and *Akkermansia* and decreases in *Butyricimonas* and correlated with variations in the expression of genes involved in dendritic cell maturation, interferon signalling, and NF-kB signalling pathways in circulating T cells and monocytes. Individuals on disease-modifying treatment showed increased abundances of *Prevotella* and *Sutterella* and decreased *Sarcina*, compared with untreated patients	Individuals with MS had alterations in the gut microbiota associated with inflammation
Case-controlled, cross-sectional,	Individuals with relapsing-remitting MS ($n = 20$) and HCs ($n = 40$)	No differences in α-diversity between groups. Individuals with MS had lower abundance	Individuals with MS had lower abundances of SCFA-producing bacteria

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
observational [146]		of *Bacteroides*, *Faecalibacterium*, *Prevotella*, *Anaerostipes*, *Clostridia* clusters *XIVa* and *IV* and increases in abundance of *Eggerthella lenta*	
Case-controlled, cross-sectional, observational [147]	MS individuals (five treated with glatiramer acetate and two with untreated MS) and HCs ($n = 8$)	Individuals with MS had increases in abundance of *Ruminococcus* and decreased abundances of *Faecalibacterium* and *Bacteroidaceae*. Vitamin D3 supplementation in untreated patients with MS increased abundance of *Akkermansia* and *Coprococcus*	Glatiramer acetate and vitamin D supplementation were associated with differences or changes in the microbiota
Amyotrophic lateral sclerosis			
Case-controlled, observational [148]	Individuals with ALS ($n = 66$) and sex- and age-matched HCs ($n = 61$) and neurodegenerative controls ($n = 12$)	The relative abundance of the dominant butyrate-producing bacteria *Eubacterium rectale* and *Roseburia intestinalis* and other species was lower in individuals with ALS	Individuals with ALS had lower abundance of SCFA-producing bacteria, associated with gut integrity and regulation of inflammation
Case-controlled, observational [149]	Individuals with ALS ($n = 50$) and sex- and age-matched HCs ($n = 50$)	Reduced α-diversity and altered relative abundances of several taxa compared to those in HCs. *Cyanobacteria*, at phylum level, and *Lactobacillus*, *Bifidobacterium*, and *Odoribacter* at genus level were more abundant in ALS individuals	Individuals with ALS exhibited an increase of potential neurotoxic or pro-inflammatory activity microbial groups such as *Cyanobacteria*
Case-controlled, observational [150]	Individuals with ALS ($n = 20$) and sex- and age-matched HCs ($n = 20$)	Increased α-diversity in ALS patients. In individuals with ALS, *Bacteroidetes* at the phylum level and several microbes at the genus level were upregulated, *Firmicutes* at the phylum level and *Megamonas* at the genus level were downregulated compared	Individuals with ALS has an altered composition of gut microbiota and metabolic products

(continued)

Table 2 (continued)

Type of study	Participants	Results	Conclusions
		to HCs. Decreased gene function associated with metabolic pathways was observed in ALS patients	
Case-controlled, observational [151]	Individuals with ALS ($n = 8$) and sex- and age-matched HCs ($n = 8$)	Individuals with ALS had increased levels of *Firmicutes*/*Bacteroidetes* ratio, genus *Methanobrevibacter*, whereas the relative abundance of beneficial microorganisms (genera *Faecalibacterium* and *Bacteroides*) were decreased. No differences between the two groups were observed in host plasma endotoxin, SCFA, NO_2-N/NO_3-N, and γ-aminobutyric acid	Individuals with ALS had an imbalance in intestinal microflora, with reduced abundance of beneficial bacteria, and increased abundance of harmful bacteria
Case-controlled, observational [152]	Individuals with ALS ($n = 25$, 2 familial, 23 sporadic) and sex- and age-matched HCs ($n = 32$)	No differences in α-diversity, β-diversity, and *Bacteroidetes*/*Firmicutes* ratio between groups. Individuals with ALS had lower abundances of *Ruminococcaceae* at genus level	The gut microbiota of individuals with ALS did not differ from healthy individuals
Case-controlled, observational [153]	Individuals with ALS ($n = 6$) and HCs ($n = 5$)	Individuals with ALS had a decreased *Firmicutes*/*Bacteroidetes* ratio, increased genus *Dorea* (harmful microorganisms), and reduced genus *Oscillibacter*, *Anaerostipes*, and *Lachnospiraceae* (beneficial microorganisms)	Individuals with ALS had an imbalance in intestinal microflora, with reduced abundance of beneficial bacteria and increased abundance of harmful bacteria

individuals is characterised by a decrease in taxonomic diversity and significant differences in the bacterial community. Overall, PD patients showed reduced levels of anti-inflammatory-associated butyrate-producing bacteria such as *Blautia* and *Roseburia* [136, 138], lower concentrations of SCFAs in faeces [135], and increased levels of pro-inflammatory-associated bacteria *Ralstonia* in the mucosa [136]. Moreover, non-significant reductions were observed for *Prevotellaceae* in PD patients, which may contribute to increased gut permeability in PD [136, 137].

Interestingly, gut microbiota alterations were linked with clinical characteristics [126, 128]. For instance, an increase in *Enterobacteriaceae* found in these patients [135, 138] positively correlated with postural instability [138] and disease severity [131]. These alterations in the microbiota of individuals with PD persisted over disease progression [125].

Together, these investigations suggest a pro-inflammatory environment in the gut of PD individuals. A bacterial metabolite, which is a marker of gut dysbiosis, was found in higher concentrations in individuals with PD [158]. On top of that, individuals suffering from PD have increased intestinal permeability that correlates with intestinal α-synuclein [159]. These findings in the gut microbiota of PD patients could be microbial biomarkers for PD used as supplemental evidence for PD diagnosis [123, 135–138].

When other facets of PD have been studied, such as the prodromal phase of PD or PD associated with mild cognitive impairment, the gut microbiota has been reported to be differently altered in comparison to individuals with PD and HCs [124], indicating that the microbiota changes alongside the progression of the disease. Thus, more studies are needed that target these phases of the disease.

6.2 AD and Microbiome

The evidence linking AD and gut dysbiosis is less pronounced than in PD. The modulation of the gut microbiome using germ-free mice, or conventional mice treated with antibiotics or probiotic administration, has shown that changes in the gut microbiota correlate with changes in host cognitive behaviours. For instance, germ-free mice exhibited impairments in spatial and working memory [160]. Temporary depletion of gut microbiota using antibiotics in rats also led to increased anxiety-like behaviours and deficits in spatial memory [161]. The administration of *Lactobacillus fermentum* NS9 reduced the alterations in behaviour induced by antibiotic treatment [161]. Moreover, administration of SCFAs promoted Aβ deposition in germ-free mice and exacerbated Aβ deposition in colonised mice via modulation of microglial phenotype [162]. As well, faecal transplantation of healthy microbiota reduced the formation of Aβ plaques and neurofibrillary tangles, glial reactivity, and cognitive impairment [163]. Thus, the role of gut microbiota in Aβ pathology and cognitive behaviour suggests that they could have a role in the pathogenesis of AD and therefore act as a novel avenue for therapeutic intervention.

Diet has long been considered linked with AD pathogenesis through the modulation of the immune system [164]. A Mediterranean diet is characterised by abundant plant-based foods such as fruits and vegetables, olive oil, and nuts as the main fat component, with a moderate intake of dairy products, fish, poultry, and eggs. Epidemiological investigations have shown that higher adherence to the Mediterranean diet correlated with a reduced risk of AD [165]. For example, omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are essential for normal brain function [166], and abundant ω-3 PUFAs in the diet of elderly populations correlated

negatively with cognitive decline [167]. Furthermore, frequent intake of fruits and vegetables, naturally high in antioxidants and vitamins, can also lower the risk of dementia and cognitive impairment [168]. Diets that are high in fats and sugars, such as the Western diet, can lead to cognitive impairment, memory decay, and increase the risk of AD [169]. High fat diets can induce changes in the gut microbiota and promote intestinal permeability, ultimately increasing inflammation, promoting disease. This suggests that gut microbiota play an important role in the increase/decrease of diet-associated AD risk. Nevertheless, the mechanisms driving the effects of gut microbiota in AD need further study.

Evidence from human studies assessing the role of the microbiome in the pathogenesis of AD is still very recent and limited. Some small case-control studies have indirectly evaluated the oral microbiome of AD individuals, as AD has long been linked to poor dental hygiene. When the gut microbiome of AD individuals was compared to healthy age- and sex-matched controls, AD individuals exhibited lower microbial diversity, decreased abundances of *Firmicutes* and bifidobacteria; moreover, levels of differentially abundant genera correlated with cerebrospinal fluid biomarkers of AD pathology [120].

Calprotectin is a protein biomarker used to assess intestinal inflammation. In a small study, AD individuals presented with a high calprotectin level in their faeces, indicating a disturbed intestinal barrier function in AD [170]. Another study comparing cognitively impaired individuals with and without amyloidosis to HCs found that the group with cognitive impairment and amyloidosis showed a lower abundance of *Eubacterium rectale* and a higher abundance of *Escherichia/Shigella*, which correlated with pro-inflammatory cytokines in blood, suggesting that those patients suffered from peripheral inflammation [119]. Another study found differences in abundance of *Bacteroides*, *Actinobacteria*, *Ruminococcus*, and *Lachnospiraceae* between AD patients and HCs [118].

Moreover, alterations in the GABAergic system are linked to cognitive impairment [171], and the evidence of GABA dysregulation in AD and ageing is substantial [172]. Interestingly, *Lactobacillus* and *Bifidobacterium* can produce GABA in the gut that can influence GABA in the CNS [173].

Although less direct, other evidence also supports the role of gut microbiota in the pathogenesis of AD. The hygiene hypothesis states that reduced microbial exposure due to improved sanitation and lifestyle changes in modern societies induces a malfunction of immunoregulation processes, contributing to autoimmune and inflammatory diseases. AD has many similarities with autoimmune diseases as it is an inflammatory disease with elevated Th1-mediated inflammation [23, 174]. When the relationship between the incidence of AD and environmental microbial diversity were investigated, countries with a greater degree of sanitation, and a lower extent of microbial diversity, had higher incidence of AD [175].

As summarised here, there are multiple connections that link AD and gut microbiome alterations, making microbiome-targeted interventions worth investigating further.

6.3 HD and Microbiome

Gut dysbiosis and increased intestinal permeability in HD are frequently reported together in both clinical and preclinical studies [140, 176, 177]. In a rodent model, although substantial changes in bacterial species abundance in the gut microbiota were not found in a longitudinal study of HD and wild-type mice, the HD gut microbiome was perturbed in the premotor symptom phase, suggesting the occurrence of gut dysbiosis in HD [178]. The sequencing data of another rodent study reinforces this subtle change in the gut microbiome of HD since they observed similar bacterial populations in HD and wild-type mice but differences in abundances [178]. In humans, it is still unclear whether individuals with HD present greater bacterial diversity in the gut, but alterations in bacterial abundances have been reported [139, 140]. For example, the abundance of *Intestinimonas* was higher in individuals with HD and correlated with HD clinical characteristics [139]; here, a correlation was established between altered gut microbiota and the occurrence of chronic inflammation [139]. Nevertheless, the alterations of the gut microbiome in HD are only recently being investigated, and a better understanding of this should become clearer in the future.

6.4 MS and Microbiome

Autoimmune diseases such as MS are characterised by a dysregulation of the immune system, and recently it was shown that the gut microbiota can modulate the immune system. For example, germ-free animals develop an attenuated experimental autoimmune encephalomyelitis (EAE) response, which is a rodent model of MS, unless they are transplanted with gut microbes from colonised mice [179], suggesting that the gut microbiota are key for disease progression. Interventional preclinical studies showed that probiotic administration can ameliorate disease severity in EAE by reducing inflammation and inhibiting Th17 cell differentiation [180, 181]. Similarly, oral administration of broad-spectrum antibiotics ameliorated EAE development in mice [182]. These data together suggest that the gut microbiome is implicated in MS pathogenic severity.

In terms of gut microbial community composition, the level of diversity between patients with MS and HCs was similar, but the relative abundances of specific bacteria differed significantly. In contrast to AD/PD, MS is not presented exclusively in an adult or elderly population, and consequently the microbiome does not necessarily have the particularities seen in an aged microbiome. Nevertheless, MS patients exhibited reduced levels of *Clostridia* family and *Bacteroidetes*, known to produce SCFAs and induce Treg cells [146], potentially facilitating autoimmune processes. Furthermore, *Methanobrevibacter smithii* and *Akkermansia muciniphila* are increased in stool samples of MS individuals, which can affect T cell differentiation [142, 145]. Moreover, excessive expansion of intestinal Th17 cells correlated

with microbiota alterations and disease activity [141]. There is strong evidence surrounding the involvement of the microbiome in MS; however, is it still unclear if the microbiome is the trigger or a driver of the neuroimmune pathogenesis.

6.5 ALS and Microbiome

ALS pathology is intricately linked to alterations in glutamate, GABA, and serotonin, and some strains of our gut microbiota can modulate the production of these neurotransmitters. Moreover, in a transgenic mouse model of ALS, the disruption of the junction structure in the intestine led to increased gut permeability, abnormal Paneth cells in the intestine [183], and reduced levels of *Butyrivibrio* (butyrate-producing bacteria) *fibrisolvens*, *Escherichia coli*, and *Firmicutes* bacteria, in comparison to wild type mice [183], suggesting microbial dysbiosis.

The gut microbiota in individuals with ALS exhibits a reduction of the ratio *Firmicutes*/*Bacteroidetes* phyla [153], which has been associated with detrimental health outcomes. In particular, butyrate-producing bacteria are reduced at early stages of the disease [183, 184]. Furthermore, ALS disease was associated with reduced levels of beneficial bacteria from the genera *Oscillibacter* and *Anaerostipes* and the family *Lachnospiraceae* and increased levels of harmful bacteria such as genus *Dorea* [153]. More evidence supports these changes in the abundance of microbial species between individuals with ALS and healthy subjects. In a randomised controlled trial, ALS patients had higher abundance of *Escherichia coli* and enterobacteria [185]. Furthermore, gut microbiota composition in ALS changes over the course of the disease; significant fluctuations of certain microbial strains were observed in a longitudinal study [149]. Overall, recent studies support the idea that relative abundance of beneficial microorganisms is decreased in ALS [151, 183, 185, 186]. On top of that, a higher vegetable fibre intake was shown to be associated with a slower-progression ALS disease [187].

Microbiota signatures as an element in the aetiology or pathogenesis of the disease have been broadly discussed [188, 189] and have led to investigative approaches towards modulating the gut microbiota in ALS patients as a novel therapeutic. Furthermore, these human studies have not only helped characterise the gut microbiota of ALS patients during the progression of the disease, but they are also the basis for a characterisation of these microbiota changes into an ALS biomarker.

In summary, host gut microbiota of neurodegenerative disease patients is markedly different than healthy subjects and is characterised by an overgrowth of pathogenic and reduction of commensal microbial strains, leading to altered production of beneficial metabolites such as SCFAs, which eventually increases the pathogenic milieu, setting up a vicious cycle. The development of gut microbiota-targeted interventions could help disrupt this endless loop of pro-inflammation and ameliorate at least some of the pathophysiological events, benefiting the patient.

7 Microbiota-Targeted Therapeutic Interventions for Neurodegenerative Diseases

In the search for therapeutic interventions for neurodegenerative disease, much effort has gone into trying to halt or reduce the aggregation of the aberrant protein involved, as well as directly targeting the pathways that lead to neurodegeneration, such as neuroinflammation. Microbiome modulation is an innovative approach that could address those targets indirectly and provide novel microbiome-targeted interventions for these diseases. Directly targeting neuroinflammation through the gut microbiota is one of the most common objectives of these therapeutic investigations. Evidence highlighting the role of gut microbiome in neurodegeneration has uncovered new insights in potential microbiome-based therapeutic approaches, interventions not only targeted to the direct modulation of the gut microbiota but also to their metabolites such as SCFAs.

Therapies include the use of antibiotics, probiotics, prebiotics, and FMT. Below we summarise some of the investigations carried out to date, regarding the potential of the gastrointestinal microbiota and metabolites, to ameliorate some facets of neurodegenerative diseases.

7.1 Microbial Metabolite-Based Interventions

SCFAs are neuroactive biomolecules and as such have a potential interest as a therapeutic agent for neurodegenerative disease. Although the specific signalling around neuroprotective and anti-inflammatory effects of SCFAs are not completely understood, it has thus far been attributed, at least in part, to their histone deacetylase (HDAC) inhibitory action. First, SCFAs are well known to have anti-inflammatory effects [190] and to be involved in the modulation of microglial function [115]. For example, butyrate can decrease microglial activation and pro-inflammatory cytokines in vivo [191, 192]. Second, SCFAs are able to modulate neurotransmitter synthesis and expression. For example, butyrate and propionate can control catecholamine synthesis by regulating tyrosine hydroxylase gene expression [193]. This is very interesting for PD research in particular, as tyrosine hydroxylase is an enzyme involved in dopamine synthesis. Moreover, SCFAs can modulate the concentrations of other neurotransmitters such as glutamate, glutamine, and GABA [194].

These promising neuroprotective and anti-inflammatory properties make SCFAs a good candidate for a potential therapeutic agent in neurodegenerative diseases; for example, HDAC dysregulation has been implicated in memory impairment, and levels of SCFAs are reduced in preclinical models of AD [195]. In a rodent model of AD, sodium butyrate was able to improve associative memory and increase expression of genes associated with learning even at advanced stages of pathology [196]. Butyrate has also shown promising beneficial effects in improving cognitive and motor impairments while reducing dopamine neurodegeneration in several

animal models [197, 198]. If we look at MS, oral administration of SCFAs ameliorated the disease severity in an EAE model [199], and butyrate in particular was able to suppress demyelination and enhance remyelination [200].

SCFAs can also exert anti-inflammatory effects via astrocytes, as SCFAs downregulate the astrocytic production of IL-1β and TNF-α [201]. Further, SCFAs can also contribute to reduce inflammation by inhibition of NF-kB on peripheral blood mononuclear cells, which further reduces the production of pro-inflammatory cytokines [202].

These results provide strong evidence that SCFAs can regulate several CNS processes related to neurodegeneration as well as modulate cognitive and motor behaviours, especially when administered in advanced stages of neurodegeneration. However, caution has to be taken when extrapolating these results to humans as these were mainly observed in animal models.

Ferulic acid (FA) is a gut-derived compound found in fruits and vegetables that can also be synthetised by gut bacteria. FA can prevent Aβ toxicity by inhibiting Aβ aggregation both in vitro and in vivo [203]. Two long-term studies assessed the benefits of oral administration of FA in transgenic mouse models of amyloidosis and found that FA reversed spatial memory deficits, reduced Aβ aggregates in the brain, attenuated neuroinflammation, and stabilised oxidative stress [203, 204].

Dysregulation of the kynurenine pathway is associated with neurodegenerative and other neurological disorders. Targeted interventions with metabolites from the kynurenine pathway could potentially be used to modulate brain physiology and normalise imbalances in this pathway in pathological conditions. For example, indoleamine 2,3-dioxygenase (IDO) inhibitors are being investigated for their protective role against oxidative damage [205]. Since gut microbiota are a key regulator of the kynurenine pathway, probiotic products may be potentially beneficial in regulating kynurenine/tryptophan dynamics [205].

Recently, researchers manipulated disease severity in a rodent model of ALS via supplementation with gut microbial strains; where *Ruminococcus torques* and *Parabacteroides distasonis* increased severity of the disease, *Akkermansia muciniphila* ameliorated it [206]. Interestingly, this reduction of the pathogenesis by *Akkermansia muciniphila* was attributed to increasing levels of nicotinamide, together with changes in mitochondrial function and oxidative stress pathways. Moreover, nicotinamide was associated with functional improvements in ALS patients [207]. Also the therapeutic potential of hydrogen sulphide and molecular hydrogen was tested in mice; it was shown that hydrogen-rich saline administration could preserve mitochondrial function and reduce ROS production [208].

7.2 Probiotic-Based Interventions

Probiotic interventions are being screened in several contexts including neuroprotection, neurodegeneration, and inflammation. These studies inform us of the potential of these probiotic products (see Table 3). For example, a combined

Table 3 Clinical studies assessing microbiota-based interventions for neurodegenerative diseases

Type of study	Intervention	Results
Alzheimer's disease		
Double-blind, randomised, controlled [209]	Patients were given milk ($n = 30$) or a probiotic ($n = 30$) containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* for 12 weeks	Probiotic treatment resulted in improvements in cognitive function scores and a significant change in metabolic profile
Double-blind, randomised, placebo-controlled [210]	Patients were given either selenium (200 μg/day) plus probiotic containing *L. acidophilus*, *B. bifidum*, and *Bifidobacterium longum* ($n = 27$), selenium (200 μg/day) ($n = 26$), or placebo ($n = 26$) for 12 weeks	Co-supplementation of selenium and probiotic treatment resulted in improvements in cognitive function scores and improvements in some metabolic profiles
Double-blind, randomised, placebo-controlled [211]	Patients were given placebo ($n = 23$) or a probiotic ($n = 25$) containing *L. fermentum*, *Lactobacillus plantarum*, *L. acidophilus*, *Bifidobacterium lactis*, *B. longum*, and *B. bifidum* for 12 weeks	No significant changes in cognitive deficit scales or biochemical measurements between probiotic and placebo groups
Parkinson's disease		
Double-blind, randomised, placebo-controlled [212]	Patients were given a placebo ($n = 60$) or a fermented milk ($n = 80$), containing multiple probiotic strains and prebiotic fibre for 4 weeks.	Probiotic and prebiotic treatment resulted in a significant increase in complete bowel movements in patients with PD compared with patients in the placebo group
Double-blind, randomised, placebo-controlled [213]	Patients were given placebo ($n = 38$) or probiotic capsules ($n = 34$) containing *L. acidophilus*, *L. reuteri*, *Lactobacillus gasseri*, *Lactobacillus rhamnosus*, *B. bifidum*, *B. longum*, *Enterococcus faecalis*, and *Enterococcus faecium* for 4 weeks	Probiotic treatment resulted in the reduction of constipation (increased spontaneous bowel movements)
Double-blind, randomised, placebo-controlled [214]	Patients were given placebo ($n = 30$) or probiotic capsules ($n = 30$) containing *L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* for 12 weeks	Probiotic treatment resulted in improvements in motor function scores and significant improvements on metabolic profiles
Double-blind, randomised, placebo-controlled [215]	Patients were given placebo ($n = 25$) or probiotic capsules ($n = 25$) containing *L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* for 12 weeks	Probiotic supplementation improved gene expression of some pro-inflammatory markers (IL-1, IL-8, TNF-α, TGF-β, and PPAR-γ) but did not change biomarkers of inflammation and oxidative stress
Double-blind, randomised, placebo-controlled [216]	Patients were given fermented milk as placebo ($n = 26$) or probiotic capsules ($n = 22$) containing *L. acidophilus*, *L. casei*, *L. lactis*,	Probiotic treatment resulted in the reduction of constipation (increased gastrointestinal time). No changes

(continued)

Table 3 (continued)

Type of study	Intervention	Results
	B. infantis, and *B. longum* plus 2% fructooligosaccharide and lactose for 8 weeks	were observed in motor function scores
Multiple sclerosis		
Double-blind, randomised, placebo-controlled [217]	Patients were given placebo ($n = 30$) or a probiotic capsule ($n = 30$) containing *L. acidophilus*, *Lactobacillus casei*, *B. bifidum*, and *L. fermentum* for 12 weeks	Probiotic intake improved disability, general health, and depression scales as well as parameters of inflammatory factors and markers of insulin resistance
Double-blind, randomised, placebo-controlled [218]	Patients were given placebo ($n = 30$) or a probiotic capsule ($n = 30$) containing *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* for 12 weeks	Probiotic supplementation improved gene expression of some pro-inflammatory markers (IL-8, TNF-α) but not others
Controlled [219]	Patients ($n = 9$) and controls ($n = 13$) were orally administered with a probiotic containing *Lactobacillus paracasei*, *L. plantarum*, *L. acidophilus*, *Lactobacillus delbrueckii bulgaricus*, *B. longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, and *Streptococcus thermophilus* twice daily for 2 months	Probiotic administration increased the abundance of taxa known to be reduced in patients with MS such as *Lactobacillus* and decreased abundance of taxa associated with dysbiosis such as *Akkermansia*, *Dorea*, and *Blautia*
Double-blind, randomised, placebo-controlled [220]	Patients were given placebo ($n = 24$) or a probiotic capsule ($n = 24$) containing *B. infantis*, *B. lactis*, *Lactobacillus reuteri*, *L. casei*, *L. plantarum*, and *L. fermentum* for 12 weeks	Probiotic intake improved disability, general health, and depression scales as well as parameters of inflammatory factors

administration of *Lactobacillus helveticus* and *Bifidobacterium longum* in a myocardial infarction model reduced pro-apoptotic pathways (caspase-3 and Bax/Bcl-2) and increased anti-apoptotic pathways (Akt phosphorylation), suggesting a role in neuroprotection [221]. *Clostridium butyricum* was also reported to have neuroprotective effects in a vascular dementia model in rats by increasing brain-derived neurotrophic factor (BDNF), Bcl-2, and Akt phosphorylation [222].

Moreover, probiotic administration can modulate long-term memory. In a rodent AD model, administration of *Lactobacillus* and *Bifidobacterium* strains improved memory and learning outcomes and reduced oxidative stress in the hippocampus [223]. In a similar study, along with behavioural recovery and a reduction of Aβ plaques, a probiotic mix formulated of lactic acid bacteria and bifidobacteria was able to partially restore proteasome and autophagy functionality [224]. In a recent study using APP/PS1 transgenic mice, exercise training and probiotic administration reduced Aβ plaques in the hippocampus and improved cognitive performance in a

spatial learning task [225]. Such investigations demonstrate that disease progression could potentially be ameliorated by microbiota-targeted approaches.

For instance, probiotics could reduce duration of the clinical symptoms or reduce their severity, while also reducing levels of pro-inflammatory cytokines in the EAE rodent model of MS [226]. Similarly, a combination of *Lactobacillus* strains produced these same effects by inhibiting pro-inflammatory activation of Th17 cells, while enhancing IL-10^{+} producing regulatory T cells [227].

Hence, preclinical investigations have shown the potential use of probiotics as a therapeutic strategy against neurodegeneration. However, few clinical investigations have been carried out to date investigating the potential benefits of probiotic products in neurodegenerative diseases (see Table 3). Overall, these clinical trials have shown that probiotic products can modulate gut microbiota composition, ameliorate comorbidities such as constipation, and even improve cognitive and motor deficits.

However, there are few clinical trials available to date, with low numbers of patients, and they only assessed the effects of short-term use of probiotics. Moreover, the results of these clinical trials are based on limited analysis of the microbiome and the cognitive and motor functions. Nevertheless, they are a first step into the evaluation of probiotics as a potential therapeutic avenue for neurodegenerative diseases and their comorbidities.

7.3 Antibiotic-Based Interventions

Antibiotic administration is another effective means of gut microbiome modulation. In vitro, many antibiotics can prevent or reduce protein aggregation in the context of neurodegenerative disease. Further, antibiotics such as ceftriaxone—which is a β-lactam antibiotic—have been shown to have neuroprotective and anti-inflammatory effects in many neurodegenerative diseases. For instance, in an AD transgenic mouse model, ceftriaxone reduced the increased levels of glutamate present in the vicinity of Aβ plaques and restored neuronal activity via glutamate transporter 1 [228]. There are several mechanisms by which ceftriaxone could act, including upregulation of glutamate transporter 1 expression, as well as the amelioration of oxidative stress and neuroinflammation [229]. Preventive and therapeutic treatment of ceftriaxone in an EAE mouse model indirectly hampered T cell proliferation and pro-inflammatory cytokine secretion [230]. Thus, antibiotic treatment can attenuate disease course and severity in a rodent model of MS.

Rifampicin inhibited the aggregation and fibril formation of synthetic Aβ peptides [231]. Similarly, doxycycline induced remodelling of α-synuclein oligomers into non-toxic species in vitro [232] and prevented Aβ fibrillisation both in vitro and in vivo [233]. Moreover, a combination of long-term broad-spectrum antibiotics decreased Aβ plaque deposition in a rodent model [234]. However, when doxycycline and rifampicin (alone or in combination) were tested in clinical trials, they had no beneficial effects on cognition in AD patients [235]. However, eradication of

Helicobacter pylori resulted in improvement of cognition outcomes in AD patients [236] and in motor improvements in PD patients [237]. These results indicate that antibiotic administration could be an interesting therapeutic option for particular cases dealing with detrimental bacteria, instead of using of antibiotics as a universal therapy for all neurodegenerative diseases.

AD might be the best candidate to test antibacterial drugs on since it has been postulated that it could have an infectious aetiology. Thus, testing antibiotics in clinical trials could shed some light onto this issue and verify if antibacterial therapy could be beneficial for a subset of (or all) AD patients [238].

7.4 Faecal Microbiota Transplantation

FMT can reconstruct the healthy gut microenvironment and alleviate clinical symptoms of many metabolic, autoimmune, and neuropsychiatric diseases. Recently, FMT has been postulated as a potential therapeutic intervention to restore the microbiome in neurodegenerative disease. Despite limited information about its long-term benefits and risks, some case reports have confirmed the efficacy of FMT for use in the treatment of neurological disorders [239]. In MS, two case reports have shown amelioration or stabilisation of MS symptoms several years after the transplant [240, 241]. In PD, one report stated that a PD patient observed improvements in constipation until the end of the follow-up 3 months after FMT, but no long-term motor improvements [242]. In a more recent study, 15 PD patients were exposed to a colonic or nasointestinal FMT and concluded that although both procedures were safe, colonic FMT achieved significant improvement and longer maintenance of efficacy than nasointestinal FMT [243]. In this study, two patients reported self-satisfying outcomes that lasted for more than 2 years [243]. In AD, there is only one case reported of a patient with rapid reversal of AD symptoms following FMT for recurrent *Clostridioides difficile* infection [244].

Currently, there are two randomised double-blind clinical trials assessing the safety and efficacy of FMT for PD patients with or without constipation (NCT04854291, NCT03808389) and other minor clinical pilot studies with the same aim (NCT03876327, NCT04837313). In parallel, other FMT clinical trials are ongoing at the moment, evaluating the safety, feasibility, and efficacy of FMT in AD patients (NCT03998423) and in ALS patients (NCT03766321). We will have to wait for their findings. However, a clinical trial of FMT for MS (NCT03183869) was finalised recently, reporting that FMT did not have any serious adverse effects, but no measures of efficacy have been reported yet.

The benefits of FMT as a therapeutic intervention in neurodegenerative disease are mostly based on animal studies and only a few case reports. Despite promising results, large-scale clinical trials are needed to evaluate the efficacy of this treatment option. Numerous trials of FMT in neurodegenerative diseases are currently ongoing, and it is expected that evidence on the efficacy of FMT will increase in the near future. Furthermore, these ongoing clinical trials will improve the logistics of FMT

that still need to be refined, such as best donor selection or mode of delivery of the microbiota.

Even if microbiota-targeted interventions prove not to be successful in the goal of stopping or ameliorating the progression of neurodegenerative diseases, they could still be very beneficial in treating gastrointestinal comorbidities.

7.5 Microbiota Modulation Through Diet

Diet has a major impact on gut microbiota. Hence, it has been postulated that diet could be a beneficial avenue for treatment of neurodegenerative diseases, as they are usually characterised by a prevalent and strong microbiota dysbiosis. For example, antioxidants can directly act on gut microbiota to reduce pathogenic bacteria and increase beneficial bacteria [245]. Consequently, these beneficial bacteria can produce beneficial metabolites for brain health, conferring neuroprotection.

Many dietary compounds such as PUFAs, vitamins B and D, or resveratrol have been found to be beneficial with anti-inflammatory properties [246]. In ALS, many preclinical investigations have shown that polyphenols such as resveratrol or curcumin could improve the prognosis of the disease [247]. Some compounds such as vitamin C have largely been investigated in preclinical studies as a treatment option for neurodegenerative disease, but clinical data in humans are limited [248].

However, a growing body of evidence points to the combination of these compounds as a more efficient way to fight neurodegeneration. Clinical and preclinical data assessing dietary interventions for neurodegenerative disease is extensive and has mostly been studied in AD. For example, the ketogenic (high-fat and low-carbohydrate) diet forces the brain to use fatty acids as the main source of energy and alter energy metabolism mechanisms. These metabolic changes reduce the usage of impaired glucose metabolism in neurodegenerative pathologies and neuroinflammation, while improving mitochondrial function, thus conferring neuroprotection to ageing brain cells [249]. In addition, this diet could help to reduce the accumulation of amyloid plaques. Two clinical trials assessed the effects of triglyceride administration on AD patients, resulting in improved cognitive outcomes [250, 251].

Further, adherence to a Mediterranean-styled diet could be a potential preventive therapy as it confers a reduced risk of developing AD and cognitive impairment [252, 253]. Moreover, it has been hypothesised that the Mediterranean diet—abundant in antioxidants, vitamins, flavonoids, polyphenols, and probiotics—could attenuate neuroinflammation via the gut microbiome. The Mediterranean dietary approach to systolic hypertension (DASH) diet intervention for neurodegenerative delay (MIND) diet (that combines Mediterranean and DASH diets) is specific for dementia prevention and can slow cognitive decline [254]. Although clinical trials have shown interesting results, there is a paucity of data surrounding the long-term benefits of these interventions in patients with neurodegenerative disease.

8 Conclusions

Neurodegenerative diseases are a heterogeneous group of disorders where neurons degenerate and ultimately die. These diseases have an unknown cause and include many complex pathological processes that have frustrated the development of a remedy or cure to stop neurodegeneration. However, the scientific knowledge gathered has greatly expanded our general understanding and treatment of neurodegenerative disease. The expert view has shifted from being neuron centric to a more global disease where even entities such as the gut microbiota are now considered.

Gut microbiota have been shown to be implicated in the pathogenesis of neurodegenerative disease, although to what extent remains to be elucidated. It is quite likely that single bacterial perturbations will not be adequate, and perhaps there will not even be a disease-specific bacterial signature but rather an overall alteration of the microbial gut environment. Nevertheless, a new era of potential microbiota-targeted interventions has emerged.

Despite numerous failures in developing therapeutic interventions that can effectively modify the course of the disease, researchers have now new molecular tools to investigate the underlying pathogenic mechanisms involved and assess the efficacy of new compounds or therapeutic interventions. Currently, the evidence supporting a beneficial impact on neurodegeneration due to microbiome modification is limited.

It will be interesting to observe if psychobiotics are assessed in neurodegenerative diseases in the future. Psychobiotics are live organisms that can produce health benefits in patients suffering from psychiatric illnesses through the microbiota-gut-brain axis [255].

The evidence that gut microbiota may be involved in the onset or progression of many neurodegenerative diseases is increasing rapidly, but causality has not been proven. However, gut microbiota could be used as a clinical biomarker for the diagnosis of many neurodegenerative diseases. Furthermore, there is an opportunity to establish potential microbiome-targeted therapies to treat particular aspects of neurodegenerative disease, such as common comorbidities, resulting in improvements of host health.

Nevertheless, adequately powered longitudinal studies are needed to investigate the complex relationship between neurodegenerative disease and the microbiome and should be studied at the onset, the initial progression, and the establishment of the neurodegenerative processes. Of high importance would be the appropriate selection of patients and adequate management of confounding variables. Many factors that were overlooked in traditional neurological studies could have confounding effects in the microbiome field. This could present opportunities for interdisciplinary approaches for the treatment of neurodegenerative disease.

Compliance with Ethical Standards

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