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REVIEW

# Interplay among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system: a common path to neurodegenerative diseases?

**Carolina Pellegrini[1] · Luca Antonioli[1] · Rocchina Colucci[2] · Corrado Blandizzi[1] · Matteo Fornai[1]**

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**Abstract**
Neurological diseases, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis, are often associated with functional gastrointestinal disorders. These gastrointestinal disturbances may occur at all stages of the neurodegenerative diseases, to such an extent that they are now considered an integral part of their clinical picture. Several lines of evidence support the contention that, in central neurodegenerative diseases, changes in gut microbiota and enteric neuro-immune system alterations could contribute to gastrointesinal dysfunctions as well as initiation and upward spreading of the neurologic disorder. The present review has been intended to provide a comprehensive overview of the available knowledge on the role played by enteric microbiota, mucosal immune system and enteric nervous system, considered as an integrated network, in the pathophysiology of the main neurological diseases known to be associated with intestinal disturbances. In addition, based on current human and pre-clinical evidence, our intent was to critically discuss whether changes in the dynamic interplay between gut microbiota, intestinal epithelial barrier and enteric neuro-immune system are a consequence of the central neurodegeneration or might represent the starting point of the neurodegenerative process. Special attention has been paid also to discuss whether alterations of the enteric bacterial-neuro-immune network could represent a common path driving the onset of the main neurodegenerative diseases, even though each disease displays its own distinct clinical features.

**Keywords** Gut microbiota · Intestinal mucosal barrier · Enteric neuro-immune system · Gut–brain axis · Patients · Animal models · Neurodegenerative diseases

## Introduction

Neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), are often associated with functional gastrointestinal (GI) disorders, including infrequent bowel movements, abdominal distension and constipation, which impact negatively on patients' quality of life, thus contributing to the morbidity of these diseases and complicating their clinical management [4, 66, 74]. Of note, GI disturbances in neurological disorders may occur at all stages of the neurodegenerative process, to such an extent that they are now considered as an integral part of their clinical picture [78].

Several lines of evidence support the contention that, in central neurodegenerative diseases, imbalances of the neuro-immune brain–gut axis could lead to the occurrence of enteric neuroinflammatory conditions and GI dysfunctions [69, 70]. Others, in keeping with the Braak's hypothesis on the pathogenesis of PD, claim that central neurodegenerative diseases could start in the enteric nervous system (ENS) and spread upwards progressively to the central nervous system (CNS), through the nerve pathways connecting the gut to the brain (i.e., the vagus nerve) [21]. In this regard, the accumulation of α-synuclein (α-syn, a hallmark of PD) in myenteric neurons represents one of the earliest signs of the disease, which could contribute to the development of GI

✉ Carolina Pellegrini
carolina.pellegrini87@gmail.com

[1] Unit of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 55, 56126 Pisa, Italy

[2] Department of Pharmaceutical and Pharmacological Sciences, University of Padova, 35131 Padova, Italy

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disturbances and to the subsequent upward spreading of PD pathology through a prion-like transmission among neurons [87, 100]. There is also increasing evidence suggesting that changes in gut microbiota composition may contribute to GI disturbances and to the pathogenesis of several neurodegenerative diseases [97]. Indeed, PD, AD, ALS and MS patients display different colonic bacterial composition than healthy controls, with a shift towards a pro-inflammatory profile [5, 13, 26, 50, 101].

Based on the above background, the present review has been intended to provide a comprehensive overview of current knowledge on the role played by enteric microbiota, mucosal immune system and ENS, considered as an integrated network, in the pathophysiology of the main neurological diseases, including PD, AD, ALS and MS and their associated intestinal disturbances. In addition, based on current human and pre-clinical evidence, our intent was to critically discuss whether changes in the dynamic interplay between gut microbiota, intestinal epithelial barrier and enteric neuro-immune system are a consequence of central neurodegeneration or represent the starting point of the neurodegenerative process. Special attention has been paid also to discuss whether alterations of the enteric bacterial-neuro-immune network could represent a common path driving the onset of the main neurodegenerative diseases, even though each disease displays distinct clinical features.

## Role of interactions among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system in the maintenance of gastrointestinal homeostasis

A dynamic interplay among the gut microbiota, intestinal epithelial barrier and enteric neuro-immune system contributes to the maintenance of digestive homeostasis (Fig. 1) [58]. Indeed, abnormal changes in gut microbiota composition (dysbiosis), alterations of the intestinal epithelial barrier, uncontrolled immune responses to pathogenic stimuli and adaptive changes in the ENS represent the main factors

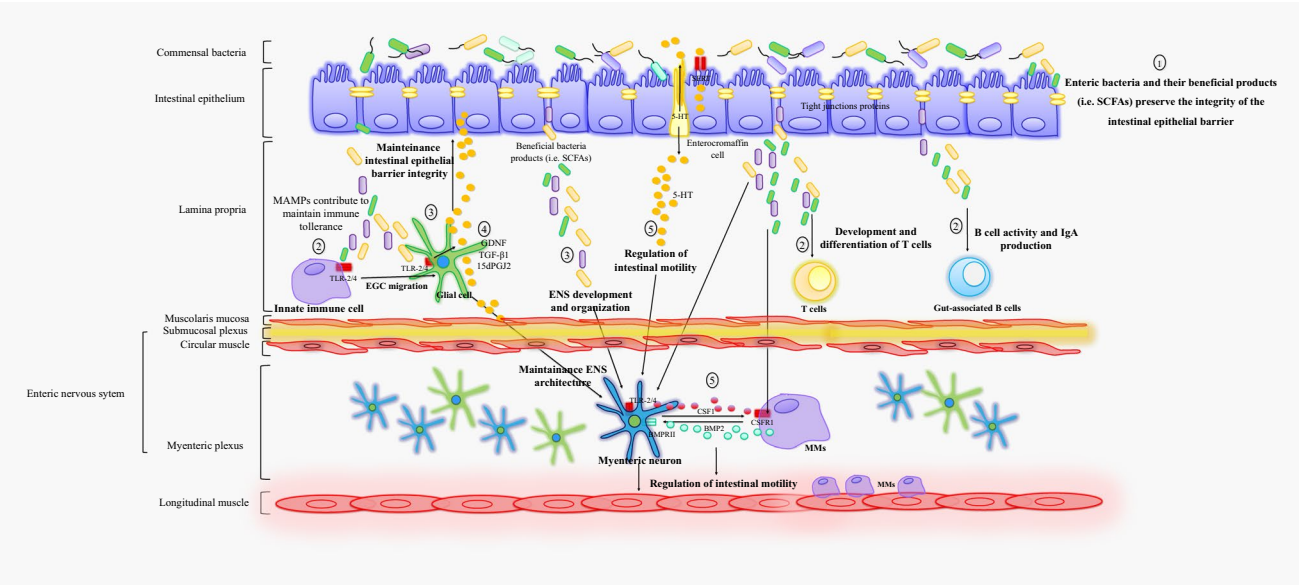


**Fig. 1** Diagram showing the physiological role of the interactions among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system. (1) Enteric bacteria and their metabolic products, mainly SCFAs, contribute to preserve the integrity of the intestinal epithelial barrier, through the regulation of epithelial cell growth and differentiation, tight junction protein expression and mucosal permeability. (2) Gut microbiota interacts directly with the enteric immune system. In particular, bacterial products (e.g., MAMPs and SCFAs) contribute to maintain intestinal immune innate tolerance. In addition, enteric bacteria can influence the development and differentiation of CD4+ and CD8+ T cells as well as B cell activity and IgA production. (3) Gut microflora influences the development and function of the ENS and EGCs. In particular, microbe-derived products through the activation of TLRs, expressed in myenteric neurons and EGCs, influence the development and organization of enteric neural networks and digestive motility. (4) EGCs, through the release of specific mediators (e.g. GDNF, TGF-β1 and 15dPGJ2 glial factor) are involved in the maintenance of both ENS and epithelial barrier integrity. (5) Gut microbiota can also regulate directly the digestive motility by stimulating the release of 5-HT from enterochromaffin cells and influencing the interplay between enteric neurons and muscularis macrophages through a regulation of the release of both CSF1 and BMP2. Abbreviation: ENS: enteric nervous system; EGCs: enteric glial cells; CSF1: colony stimulatory factor; GDNF: glial cell-derived neurotrophic factor; MMs: muscolaris macrophages; 5-HT: serotonin; SERT: serotonin-selective reuptake transporter; SCFAs: short chain fatty acids; BMP2: soluble growth factor bone morphogenetic protein; TLR: toll-like receptor; MAMPs: microbe-associated molecular patterns; 15dPGJ2: 15-deoxy-(12,14)-prostaglandin J2 glial factor; TGF-β1: transforming growth factor beta-1

implicated in the pathogenesis of several bowel disorders (e.g., inflammatory bowel diseases, irritable bowel syndrome and other functional digestive disorders) [99, 114]. In this context, the gut microbiota is currently regarded as a key player, and through interactions with all the other components, it regulates both the maintenance and breakdown of gut homeostasis [15, 114].

The gut microbiota consists of more than one trillion of microorganisms, including bacteria, viruses, fungi and protozoans. The dominant bacterial species in the GI tract are fairly stable and comprise four main phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria [80]. Enteric bacteria interact directly with the intestinal epithelium, which, together with the mucus layer, represents a barrier interposed between the luminal contents and the underlying immune, neuronal and muscular compartments [3]. The intestinal epithelium consists of several subsets of epithelial cells, which are tightly bound together by intercellular junctional complexes (e.g., tight junction proteins, such as occludin, zonulin-1 and claudins, gap junctions, adherent junctions, and desmosomes) that ensure the epithelial barrier integrity and regulate the paracellular permeability [35]. Enteric bacteria (e.g. *Faecalibacteria)* and their metabolic products, mainly short chain fatty acids (SCFAs), contribute directly to preserve the integrity of the intestinal epithelial barrier, through the regulation of cell growth and differentiation, tight junction protein expression and mucosal permeability [88]. Indeed, specific changes in gut microbiota composition can lead to a disruption of intestinal epithelial barrier and increase in mucosal permeability, with consequent bacterial translocation into the mucosa and possible systemic dissemination [3] (Fig. 2).

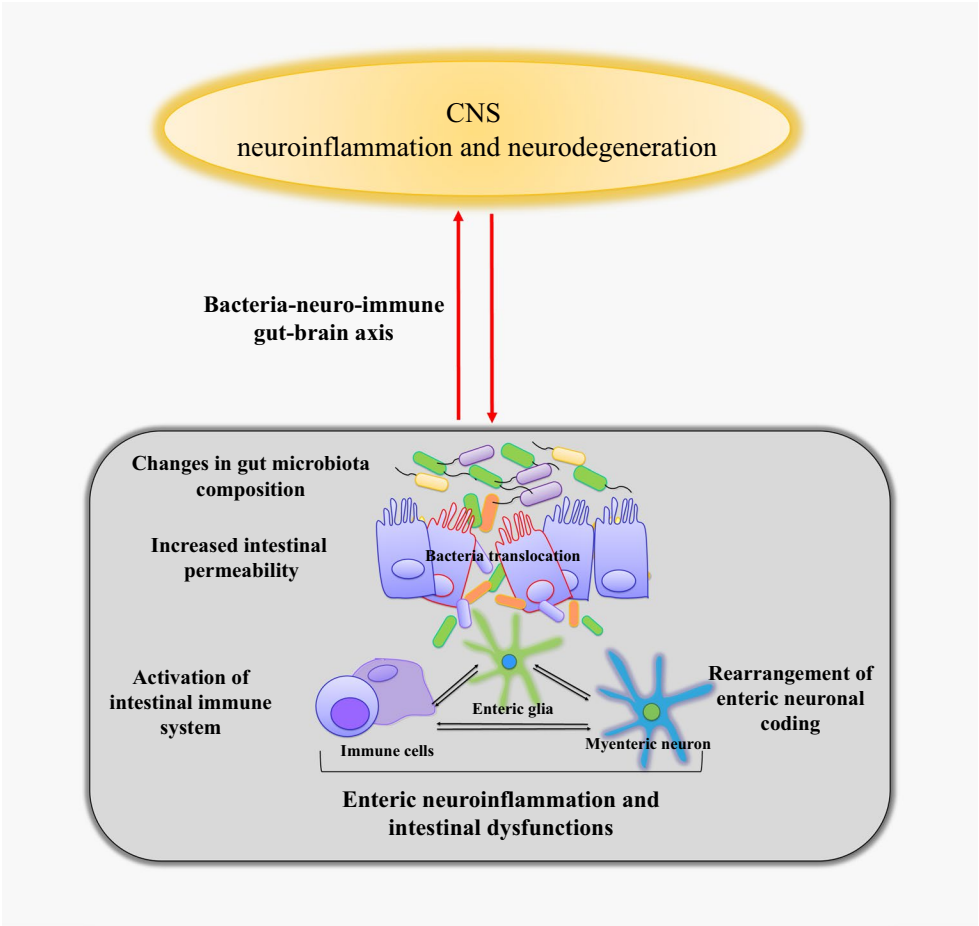


**Fig. 2** Diagram showing the common pathophysiological intestinal paths to the main neurodegerative diseases, including PD, AD, ALS and MS. In particular, gut dysbiosis and an increased intestinal permeability can promote enteric neuro/inflammatory events that, besides the induction of bowel motor dysfunctions, could trigger, via gut-brain ascending pathways, neuroinflammation and neurodegeneration in CNS. In this setting, central neuroinflammation and subsequent neurodegeneration could contribute to exacerbate enteric neuro-immune/inflammatory conditions via brain-gut descending pathways, in a sort of a positive loop that could drive the chronicization of the ongoing neuroinflammatory process. *ALS* amyotrophic lateral sclerosis, *AD* Alzheimer's disease, *MS* multiple sclerosis, *PD* Parkinson's disease

Besides the intestinal epithelium, gut microbiota interacts directly with the enteric immune system, contributing to the maintenance of immune tolerance and shaping the immune responses during inflammation [90].

Under eubiotic conditions, microbe-associated molecular patterns (MAMPs), expressed by gut microbiota, activate pattern recognition receptors, such as transmembrane surface or endosome toll-like receptors (TLRs), on innate immune cell surface, inducing the secretion of anti-inflammatory mediators, which contribute to maintain intestinal immune tolerance [58]. Conversely, upon pathogen invasion, dysbiosis or barrier break, MAMPs stimulate macrophages and dendritic cells to produce pro-inflammatory cytokines that, in turn, activate adaptive immune cells, thus contributing to the breakdown of immune homeostasis [58]. Besides innate immune cells, enteric bacteria can directly affect adaptive immune responses [8]. The main components of the adaptive immune system are T cells, in particular CD4 + and CD8 + T cells [105]. Upon stimulation, naive CD4 + T cells can differentiate into seven subtypes: T helper 1 (Th1), Th2, Th9, Th17, Th22, regulatory T cells (Treg) or T follicular helper (Tfh) cells, which express different arrays of transcription factors and cytokines [105]. The gut microbiota influences the development and differentiation of both CD4+ and CD8+ T cells. Indeed, germ-free (GF) mice display a marked decrease in the number of both CD4+ and CD8+ T cells, and treatment with SCFA mixtures is associated with an increase in the density of T cells [91, 105]. Taken together, these findings suggest that the gut microbiota and the enteric immune system interact continuously to maintain a complex dynamic equilibrium supporting the intestinal homeostasis.

Emerging evidence suggests that the gut microflora influences the development and function of the ENS [67]. Indeed, changes in gut microbiota composition or a full ablation of enteric bacteria in mice are associated with a substantial decrease in the density of myenteric neurons and the occurrence of bowel motor dysfunctions, suggesting that enteric bacteria are significant determinants of ENS trophism [59]. The ENS, consisting of the myenteric (or Auerbach's) and the submucosal (Meissner's) plexus, is an intrinsic neuronal semiautonomous network, which regulates digestive functions (e.g., motility and secretion) and cooperates with the CNS through sympathetic and parasympathetic pathways [32]. An important component of the ENS is represented by enteric glial cells (EGCs), which are associated with both submucosal and myenteric neurons [33]. EGCs are located also in proximity to epithelial cells and their terminal endfeet processes run to the epithelial basement membrane and blood capillaries [111]. Of note, EGCs, through the release of specific mediators (e.g., glial cell-derived neurotrophic factor [GDNF], transforming growth factor [TGF] β1 and 15-deoxy-(12,14)-prostaglandin J2 [15dPGJ2] glial factor) are pivotally involved in the maintenance of both ENS and epithelial barrier integrity [1, 64]. In addition, EGCs coordinate signal propagation from and to myenteric neurons and epithelial cells, thus regulating the bowel motility as well as the secretory and absorptive functions of enteric epithelium [111]. The gut microbiota is also able to regulate the initial colonization of EGCs in the intestinal mucosa [48]. Indeed, GF mice show a marked decrease in the density of mucosal EGCs [48]. The molecular mechanisms underlying the enteric bacteria-ENS interplay rely mainly on TLRs, in particular TLR-2 and -4, expressed in myenteric neurons and EGCs. Once activated by microbe-derived products, these receptors influence the development and organization of enteric neural networks as well as chloride secretion and digestive motility [10].

Overall, the interplay among gut microbiota, intestinal epithelial barrier, enteric immune system and ENS gives rise to a dynamic network aimed at coordinating the GI physiology and preserve the integrity of gut microenvironment. Interestingly, over the last years, the enteric bacteria-neuro-immune system has also emerged as a pivotal network involved in a plethora of physiological functions ranging from energy balance and metabolism to the modulation of adipose tissue, liver, skeletal muscle and brain functions [31, 36, 104]. In support of this view, gut dysbiosis, morphofunctional alterations of the intestinal epithelial barrier, activation of immune/inflammatory cells and neuroplastic changes in the ENS, besides representing main factors underlying intestinal inflammatory diseases, have been associated directly with the pathogenesis of several extra-digestive diseases (e.g., obesity, type 2 diabetes, immune-mediated diseases and neurological disorders) [31, 67, 92, 104]. Therefore, it is conceivable that the interactions among gut microbiota, intestinal epithelial barrier and enteric neuro-immune system, besides preserving the integrity of gut microenvironment, contribute also to coordinate several extra-digestive physiological processes of the host [31, 36, 104].

## Role of the interactions among gut microbiota, intestinal mucosal barrier, immune system, enteric nervous system and vagus nerve in the maintenance of brain homeostasis

A growing body of evidence highlights the relevance of gut microbiota and its interactions with intestinal mucosal barrier, immune system and ENS-vagus nerve pathways in the maintenance of brain homeostasis [30, 31]. Indeed, alterations of enteric bacteria, besides determining the breakdown of intestinal homeostasis, have been found to affect several brain biological processes (e.g., development and

neurogenesis) and behavior (e.g., anxiety, depression, learning and memory) [26, 55, 60, 97]. In this regard, a number of exhaustive review articles have provided already well-integrated overviews about the role of gut microbiota and its interactions with endocrine-neuro-immune pathways in the maintenance of brain homeostasis [20, 31, 57, 96, 97]. Therefore, in this section, we discuss briefly the most prominent data about the role of gut microbiota in the regulation of several physiological processes in the CNS, and provide an overview of the main hypothesized mechanisms underlying the microbiota gut–brain (MGB) communications.

Most of current evidence, supporting the influence of enteric bacteria on CNS functions, comes from preclinical studies on GF mice [55]. In a recent study, Erny et al. [25] observed that GF mice displayed an altered density, morphology and maturity of microglia, the most abundant resident immune cells in the brain, involved in neurodevelopment, phagocytosis, antigen presentation, cytokine production and activation of inflammatory responses [63]. In particular, microglial cells in GF mice were characterized by longer processes and branching as well as an increased expression of colony-stimulating factor 1 (CSF1) receptor, F4/80 and CD31, all these factors being known to undergo a decrease in their expression throughout the development of the brain toward an adult-stage phenotype. Moreover, the authors observed that treatment with a SCFA mixture in GF mice restored the density and morphology of microglia, thus suggesting that gut microbiota can influence both the development and functions of CNS immune cells [25]. Other pioneering studies have shown that GF mice are characterized by a decreased expression of brain-derived neurotrophic factor (BDNF), a neurotrophin involved in neurogenesis, neuronal survival, differentiation, growth, and synaptic plasticity, in the cortex, amygdala and hippocampus [34, 68, 94]. Braniste et al. [7] reported that GF animals display a decreased occludin and claudin-5 tight junction protein expression in the frontal cortex, striatum and hippocampus as well as an increased permeability of the blood–brain barrier (BBB). Moreover, they observed that the subsequent mono-colonization of GF mice with *Clostridium tyrobutyricum* or *Bacteroides thetaiotaomicron* or their treatment with butyrate increased the expression of tight junction proteins and restored paracellular permeability, thus indicating that enteric bacteria contribute to preserve the BBB integrity [7]. Taken together, these findings suggest that gut microbiota influences significantly several physiological processes in the CNS, including development, neurogenesis, neurotransmission and immune cell activity, thus contributing to the maintenance of brain homeostasis. In this context, the MGB axis, including enteric bacteria as well as endocrine, neuronal and immune pathways, is currently regarded as the key player in the regulation of mutual signaling between gut microflora and CNS [31, 55, 77, 96].

The current hypothesized mechanisms underlying MGB communications rely mainly on interactions of the gut microflora with intestinal mucosal barrier, immune system and/or ENS-vagus nerve pathways. In particular, the enteric bacteria and their metabolites (e.g., SCFAs) can stimulate directly the enterochromaffin cells to produce several neuropeptides (e.g., peptide YY, neuropeptide Y, cholecystokinin, glucagon-like peptide-1 and -2, and substance P) or neurotransmitters (e.g., serotonin), which, in turn, can diffuse into the blood stream, reach the brain and influence directly CNS functions [12]. In addition, the intestinal epithelium regulates the translocation of specific bacterial products (e.g., SCFAs, vitamins or neurotransmitters, such as acetylcholine, dopamine, noradrenaline, gamma-aminobutyric acid or serotonin) into the blood stream, which, in turn, through the circulatory system, can spread upwards to the CNS [31, 82, 103]. Therefore, it appears that circulating microbiota-derived metabolites, neuropeptides and neurotransmitters can enter the CNS and influence directly its neurobiology. Intestinal bacteria and their products can activate also intestinal and circulating innate and adaptive immune cells, which, in turn, migrate to the CNS and influence brain functions, via the brain lymphatic network, thus suggesting that the immune system contributes to communications across the MGB axis [54, 81]. However, the mechanisms through which immune cells coordinate the gut–brain axis remain still poorly understood and deserve extensive future investigations.

Of note, gut microbiota has been found to interact with ENS-vagus nerve pathways [32]. In particular, bacterial derived-neurotransmitters and neuropeptides can activate directly myenteric neurons, which, through vagal nerve ascending fibers, deliver nerve inputs to the brain [43]. In support of this view, vagotomy prevented the anxiolytic and antidepressant effects of *Lactobacillus rhamnosus* in wild-type mice [9]. However, the mechanisms underlying gut microbiota-ENS-vagus nerve interaction remain to be clarified. In addition, there is a lack of data about the possible role of sympathetic nerve pathways connecting the gut to the brain.

Overall, the gut microbiota and its interactions with the intestinal mucosal barrier, the immune system and the ENS-vagus nerve pathways give rise to a dynamic network deputed to the coordination of brain physiology. However, future investigations are required to clarify in detail the molecular and cellular mechanisms underlying the bacteria-neuro-immune pathways connecting the gut to the brain both in health and under pathological conditions.

## Pathophysiological role of the interactions among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system in neurodegenerative diseases

Recent experimental and clinical investigations have been focused on the putative role of gut microbiota, intestinal immune system or ENS, regarded as distinct determinants, in the pathophysiology of central neurodegenerative diseases and related GI dysfunctions. However, it is being increasingly appreciated that, in this setting, gut microbiota, mucosal barrier and enteric neuro-immune system should be considered as an integrated mutually interacting network. The most prominent data on the alterations of the interplay among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system in the most common neurological diseases are addressed in the following sections and summarized in Tables 1 and 2.

**Table 1** Summary of intestinal alterations in patients with central neurodegenerative diseases

| Neurological disorder | Main changes in gut microbiota composition | Morphofunctional alterations of intestinal epithelial barrier | Intestinal neuro/immune inflammatory responses | Refs. |
|---|---|---|---|---|
| PD | ↑↓Bacteroidetes (conflicting evidence)<br>↓= Firmicutes (conflicting evidence)<br>↑*Blautia, Coprococcus, Roseburia, Escherichia coli, Akkermansia, Bifidobacterium, Flavonifractor and Lactobacillus, Christensenella, Catabacter, Oscillospira, Christensenella minuta, Catabacter hongkongensis, Lactobacillus mucosae, Ruminococcus bromii, and Papillibacter cinnamivorans*<br>↓*Ralstonia, Faecalibacterium prausnitzii, Clostridium coccoides and Bacteroides fragilis, Dorea, Bacteroides, Bacteroides massiliensis, Stoquefichus massiliensis, Bacteroides coprocola, Blautia, glucerasea, Dorea longicatena, Bacteroides dorei, Bacteroides pebeus, Coprococcus eutactus, Ruminococcus callidus*<br>↑Enterobacteriaceae, Lachnospiraceae Lactobacillaceae, Verrucomicrobiaceae<br>↓Prevotellaceae *(Prevotella copri),* Erysipelotrichaceae *(Eubacterium biforme),* Barnesiellaceae and Enterococcacea<br>↓Fecal SCFAs levels (butyrate, acetate, propionate) | No functional alterations of intestinal permeability<br>↑Occludin expression<br>No changes in ZO-1 expression<br>↑LPS serum levels | ↑Nitrotyrosine<br>↑Pro-inflammatory cytokines (TNF, IF-γ, IL-6, IL-1β)<br>Enteric glia activation (↑GFAP,↑Sox-10,↑S100-beta) | [52]<br>[91]<br>[106]<br>[29]<br>[43]<br>[44]<br>[90]<br>[3]<br>[46]<br>[76]<br>[17]<br>[18]<br>[25]<br>[31] |
| AD | ↑*Bacteroides and Blautia*<br>↓*SMB53 and Dialister* | n.a | ↑Colonic CD68 macrophages<br>↑Fecal calprotectin levels | [109]<br>[54]<br>[80] |
| ALS | ↓Firmicutes/Bacteroidetes ratio<br>↓Oscillibacter, Anaerostipes, Lachnospiraceae | n.a | n.a | [28] |
| MS | ↓Bacteroides (*Bacteroides stercoris, Bacteroides coprocola, and Bacteroides coprophilus*)<br>↑*Pseudomonas, Mycoplana, Haemophilus, Blautia, and Dorea* genera | ↑Intestinal permeability (↑Urinary mannitol concentration) | ENS nerve fiber disintegration<br>Enteric gliosis | [15]<br>[64]<br>[12]<br>[116] |

*PD* Parkinson's disease, *AD* Alzheimer's disease, *MS* multiple sclerosis, *ALS* amyotrophic lateral sclerosis, *SCFAs* short chain fat acids, *TNF* tumor necrosis factor, *IF-γ* interferon gamma, *IL-6* interleukin-6, *IL-1β* interleukin-1 beta, *GFAP* glial fibrillary acidic protein, *ZO-1* zonilun-1, *LPS* lipopolysaccharides

**Table 2** Summary of intestinal alterations in animal models of neurodegenerative disorders

| Experimental models | Gut microbiota, intestinal epithelial barrier, and enteric neuro-immune system alterations | Refs. |
|---|---|---|
| *PD* | | |
| Rotenone-induced central dopaminergic neurodegeneration | ↑Firmicutes/Bacteroidetes ratio<br>↑α-syn in myenteric neurons<br>Colonic inflammation (↑MyD88, NF-kB, TLR-2,IL-6, TNF, iNOS) | [117] |
| LPS-induced central dopaminergic neurodegeneration | ↑Intestinal permeability (↑lactulose/mannitol ratio and sucralose levels)<br>↑α-syn in myenteric neurons | [51] |
| MPTP-induced central dopaminergic neurodegeneration | Activation of intestinal MyD88/NF-kB pro-inflammatory signaling<br>Enteric neuronal loss<br>↓Enteric TH expression | [19]<br>[20] |
| *AD* | | |
| APP/PS1 mouse (genetic model of AD) | ↓Fecal SCFAs levels<br>↑Aβ protein precursor, Aβ protein, BACE-1 and p-Tau<br>Intestinal inflammation (↑luminal IgA levels, COX-2 and TIMP-1)<br>↑Intestinal CD68 macrophages<br>↓Neuronal nitric oxide synthase (nNOS) and choline acetyltransferase (ChAT) | [30]<br>[40] |
| TgCRND8 mice (genetic models of AD) | ↑Aβ protein precursor in myenteric neurons<br>Intestinal inflammation (↑TLR-4)<br>Enteric glial activation (↑GFAP, nestin)<br>Enteric neuronal loss<br>Smooth muscle cell atrophy | [92] |
| 5xFAD mice (transgenic model of AD) | ↑Firmicutes/Bacteroidetes ratio<br>↑AβPP accumulation | [7] |
| *ALS* | | |
| G93A mice (genetic model of ALS) | ↓*Butyrivibrio Fibrisolvens, Escherichia coli,* and Firmicutes<br>↑Intestinal permeability (↑FITC plasma levels and ZO-1 and e-cadherin expression)<br>↑Abnormal Paneth cells<br>Intestinal inflammation (↑IL-17 pro-inflammatory cytokine levels) | [115]<br>[123] |
| *MS* | | |
| Experimental autoimmune encephalomyelitis (EAE) | Abnormal intestinal permeability (↑plasma Na-F and FITC levels and ZO-1 expression)<br>↑Crypt depth and thickness of submucosal and muscular layers<br>↑Pro-inflammatory Th1/Th17 cells in the intestinal lamina propria<br>Enteric glial activation and neuronal loss<br>Abnormal GI motility | [69]<br>[116] |

*PD* Parkinson's disease, *AD* Alzheimer's disease, *MS* multiple sclerosis, *ALS* amyotrophic lateral sclerosis, *SCFAs* short chain fat acids, *TNF* tumor necrosis factor, *IF-γ* interferon gamma, *IL-6* interleukin-6, *IL-1β* interleukin-1 beta, *GFAP* glial fibrillary acidic protein, *ZO-1* zonilun-1, *MyD88* Myeloid differentiation primary response 88, *NF-kB* nuclear factor kB, *iNOS* inducible nitric oxide synthase, *LPS* lipopolysaccharide, *α-syn* α-synuclein, *MPTP* l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine, *TH* tyrosine hydroxylase, *COX-2* cyclooxygenase, *TIMP-1* tissue inhibitor of metalloproteinases 1, *Na-F* Sodium fluorescein, *BACE-1* proteolytic enzyme beta-site amyloid precursor protein cleaving enzyme 1, *FITC* fluorescein isothiocyanate, *GI* gastrointestinal

## Parkinson's disease

GI dysfunctions represent the most common non-motor clinical manifestations of PD and, most importantly, it has been acknowledged that such GI disturbances represent one of the earliest signs of the disease [22]. In this context, intensive research efforts have been made to achieve an integrated view about the role of gut microbiota, intestinal mucosal barrier and enteric neuro-immune system in the pathophysiology of PD and related GI disturbances.

Clinical evidence, generated through the analysis of fecal and mucosal colonic microbiota, indicates that PD patients are characterized by relevant changes in enteric bacteria composition [50, 85, 98]. Some authors found that PD patients display an expansion of Bacteroidetes along with a reduced relative abundance of Firmicutes, thus suggesting a pattern of "pro-inflammatory" dysbiosis, characterized by a decrease in "anti-inflammatory" SCFA butyrate-producing bacteria, belonging to the genera *Blautia*, *Coprococcus* and *Roseburia*, and an increase in "pro-inflammatory" bacteria

of the genus *Ralstonia* and *Faecalibacterium* [50, 85]. Conversely, others observed a reduced relative abundance of Bacteroidetes without significant variations of Firmicutes, when comparing PD patients with healthy controls [98]. The same authors reported also a significant decrease in fecal SCFA levels, including butyrate, propionate and acetate in PD patients [98]. Felice et al. [26] showed a decrease in SCFA-producing *Faecalibacterium prausnitzii,* along with an increase in the abundance of Enterobacteriaceae in PD patients [27]. Others reported that PD patients displayed an increased abundance of *Akkermansia*, *Lactobacillus*, *Bifidobacterium* and *Flavonifractor,* along with a decrease in SCFA-producing bacteria, including Lachnospiraceae [41, 42, 84, 98]. In addition, two recent studies displayed an expansion of Verrucomicrobiaceae and Lactobacillaceae, along with a reduced relative abundance of Barnesiellaceae, Enterococcaceae, Prevotellaceae and Erysipelotrichaceae in PD patients [2, 44]. Of note, Petrov et al. [72] have recently provided an integrated overview about the main alterations of gut microbiota in PD. In particular, they documented that gut dysbiosis in PD patients is mainly characterized by a reduced 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*, along with an increased abundance of *Christensenella, Catabacter, Lactobacillus, Oscillospira, Bifidobacterium, Christensenella minuta, Catabacter hongkongensis, Lactobacillus mucosae, Ruminococcus bromii,* and *Papillibacter cinnamivorans* [72]. These different patterns of changes in gut microbiota composition in PD patients could depend on different methodological approaches as well as different geographical and/or clinical background of the investigated subjects (e.g., differences in mean age, disease duration and medication status). Nevertheless, these findings suggest that gut dysbiosis in PD patients is associated with a significant decrease in SCFA levels, which, being regarded as beneficial anti-inflammatory metabolic compounds produced by gut bacteria, might compromise the intestinal epithelial barrier, facilitate immune/inflammatory responses and alter the enteric neuronal network with consequent dysregulation of intestinal motility [98]. In support of this view, morphological alterations of intestinal epithelial barrier and enteric inflammation, characterized by an increase in pro-inflammatory cytokine levels and EGC activation, have been documented in PD patients [16, 17, 23]. In particular, the activation of EGCs, referred as astrocytes in the ENS, could contribute to shape enteric immune/inflammatory responses, which, besides determining intestinal motor dysfunctions, can contribute, through the neuro-immune gut–brain axis, to neuroinflammation and consequent neurodegeneration in the CNS [16, 23]. However, these data, obtained in different clinical studies, do not allow to establish a direct and mutual relationship between gut dysbiosis, impaired intestinal barrier and enteric inflammation.

At present, only two studies have evaluated in the same cohort of PD patients putative correlations between gut dysbiosis, altered intestinal permeability and enteric inflammatory/neurogenic responses. The first study, by Forsyth et al. [29], showed that, in patients with early PD, the increase in intestinal permeability correlated with the staining of intestinal mucosa for *Escherichia coli*, tissue oxidative stress, and enteric α-syn accumulation. However, this study had some limitations, since it was performed in a small cohort of PD patients and, most importantly, the increase in intestinal permeability was fairly modest. Therefore, further investigations are needed to better clarify putative correlations between abnormal intestinal permeability, enteric inflammation and α-syn accumulation in PD. In the second study, Hasegawa et al. [41] observed that in PD patients the gut dysbiosis, characterized by an increase in the number of *Lactobacillus* and a decreased abundance of *Clostridium coccoides* and *Bacteroides fragilis,* was associated with an increase in intestinal permeability [29, 41]. Taken together, these findings allow to hypothesize that, in PD, changes in gut microbiota composition, mainly the loss of SCFA-producing bacteria, along with an increase in intestinal permeability, could shape enteric inflammatory/neurogenic responses and promote α-syn accumulation in myenteric neurons that, besides the putative induction of bowel motor dysfunctions, could promote a condition of chronic peripheral inflammation, and contribute to neuroinflammation and neurodegeneration in the CNS [76]. However, current clinical evidence does not allow to firmly establish whether the alterations of enteric bacteria-neuro-immune network contribute to the pathophysiology of PD, or whether they occur rather as a mere consequence of the initiation of central neurodegenerative processes. To better understand the pathophysiological role of enteric bacteria-neuro-immune network in intestinal dysfunctions and in the onset of central dopaminergic neurodegeneration, several research efforts have been made in animal models of PD [70]. In a recent study, Yang et al. [109] observed that, in mice with rotenone-induced PD, gut dysbiosis, characterized by an increase in Firmicutes/Bacteroidetes ratio, enteric α-syn accumulation and colonic inflammation, occurred before the onset of motor deficiencies, central neurodegeneration and formation of α-syn inclusions in the CNS, thus suggesting that alterations of the enteric bacteria-immune network represent one of the earliest signs of PD that could contribute to CNS pathology. In support of this view, Sampson et al. [83] reported that fecal transplantation from PD patients to Thy1-α-syn mice (a genetic model of PD) enhanced gut dysfunctions, motor impairment, microglia activation and

α-syn accumulation in the CNS, as compared to microbiota transplantation from healthy controls. Moreover, under GF conditions, or after bacterial depletion with antibiotics, or following treatment with SCFA mixture, Thy1-α-syn animals displayed a reduced microglia activation, a decrease in α-syn inclusions, and an improvement of motor deficits [83]. These observations suggest that changes in gut microbiota contribute to central PD pathology and related motor and GI dysfunctions and, most importantly, that treatment with antibiotics or SCFAs can promote an improvement of central and peripheral symptoms of the disease. However, the authors did not evaluate whether, besides enteric bacteria, alterations of intestinal epithelial barrier or enteric inflammatory/neurogenic responses could contribute to CNS pathology and related motor and intestinal symptoms. In this regard, it is noteworthy that animals with experimental PD induced by systemic administration of lipopolysaccharide (LPS) developed an abnormal intestinal permeability in the early phases of the disease, before α-syn accumulation in the ENS and the development of central nigrostriatal neurodegeneration [49]. In addition, Cote et al. [19] reported that, in mice with l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine (MPTP)-induced PD, the activation of myeloid differentiation primary response 88 (MyD88)/nuclear factor kB (NF-kB) pro-inflammatory signaling in intestinal innate immune cells contributed to enteric and central neurodegeneration as well as microglia activation in the CNS. Indeed, peripheral MPTP injection to MyD88 knock-out mice was not followed by enteric and central neuronal loss, indicating a pivotal role of innate immune cells in the progression of ENS and CNS neurodegeneration elicited by MPTP [18]. Moreover, a partial depletion of abdominal pro-inflammatory $M_1$ monocytes in MPTP mice, through intravenous injections of clodronate-encapsulated liposome, counteracted the decrease in tyrosine hydroxylase (TH) expression in ENS, while it did not affect microglial activation and TH neuronal loss in the CNS [19]. Taken together, these pre-clinical findings, although generated in different animal models of PD, suggest that changes in gut microbiota, an impairment of intestinal permeability and enteric inflammation represent the earliest events in PD, occurring before the onset of central neurodegeneration and formation of α-syn inclusion in the CNS.

Overall, current data from human and pre-clinical studies allow to hypothesize that changes in enteric bacteria-neuro-immune network, besides determining intestinal dysfunctions, could contribute to the onset and progression of central dopaminergic neurodegeneration. However, current evidence does not allow to establish a clear causal relationship between gut dysbiosis, altered permeability, enteric inflammation and PD pathology. In addition, there is a lack of data about the pathophysiological mechanisms through which alterations of enteric bacteria-neuro-immune network contribute to the onset of central neurodegeneration. In this context, a number of issues remain pending and deserve much attention. For instance, do alterations of intestinal permeability contribute to intestinal dysbiosis in PD? Can enteric inflammatory responses trigger inflammation in the CNS? Thus, future research efforts should be dedicated to better clarify the pathophysiological role of enteric bacteria-neuro-immune network in animal models of PD as well as in patients with GI dysfunctions at different stages of the disease.

## Alzheimer's disease

Increasing evidence supports the contention that alterations of enteric bacteria-neuro-immune network may contribute to the pathogenesis of AD [45, 46, 106]. In particular, it has been postulated that changes in gut microbiota composition can promote enteric β amyloid (Aβ) protein accumulation (a hallmark of AD), which, in turn, could shape enteric and peripheral neurogenic/inflammatory responses and contribute to neuroinflammation and neurodegeneration in the CNS [56]. In addition, Aβ protein, regarded also as a prion-like proteinaceous nucleating particle, could move through myenteric neurons and spread to the CNS, via the neuronal gut–brain axis, contributing directly to the pathogenesis of AD [73, 116]. In support of this view, a pioneering study showed that, in AD patients, changes in gut microbiota composition, mainly characterized by an expansion of *Bacteroides* and *Blautia* and a reduced relative abundance of the genera *SMB53* and *Dialister,* correlated with an increase in cerebrospinal fluid of chitinase-3-like protein 1 and phosphorylated Tau (p-Tau) levels, along with a decreased Aβ42/Aβ40 ratio, all these AD biomarkers indicating a greater disease severity and amyloid burden in the brain [101]. Leblhuber et al. [52] observed signs of enteric inflammation, characterized by an increase in fecal calprotectin levels in AD patients. With regard for the deposition of Aβ protein, Aβ protein precursor (AβPP) and p-Tau in the gut, clinical evidence is scarce and conflicting, since only two studies have documented their presence in intestinal tissues from AD patients. Joachim et al. [47] showed the presence of Aβ protein deposition in rectal tissues from two AD patients. However, this protein was also detected in one of two aged normal subjects. More recently, Puig et al. [75] observed an increased colonic Aβ protein, AβPP and p-Tau immunoreactivity in eleven AD patients. In particular, all these patients displayed the presence of Aβ protein, while the immunoreactivity for AβPP and p-Tau was detected only in five subjects [75]. Nevertheless, the lack of data concerning the patterns of Aβ protein expression in the gut of control subjects does not allow to conclude that increments of Aβ protein, AβPP and p-Tau deposition occur in the enteric tissues of AD patients. In this respect, specific investigations should be implemented to better clarify the presence of Aβ, AβPP and

p-Tau proteins in both AD patients and matched healthy controls. In addition, the above findings, obtained in different clinical studies, do not allow to establish a direct relationship between gut dysbiosis, intestinal Aβ and p-Tau accumulation and enteric inflammation and, most importantly, they fail to generate direct evidence that such alterations represent one of the earliest signs of AD that could contribute to neuroinflammation and neurodegeneration in the CNS.

Several research efforts, aimed at elucidating the role of enteric bacteria-neuro-immune network as well as intestinal Aβ protein or p-Tau accumulation in the onset of central neuroinflammation, have been made in pre-clinical models of AD. In a recent study, Brandscheid et al. [6] observed that 5xFAD mice (a transgenetic model of AD) displayed changes in the gut microbiota composition, mainly characterized by an increase in Firmicutes/Bacteroidetes ratio, and intestinal AβPP accumulation since the earliest stages of the diseases. In a subsequent study, Shen et al. [89] showed that gut dysbiosis in APP/PS1 mice (a genetic model of AD) correlated with an increase in Aβ protein levels in the CNS and relevant behavioral alterations. In addition, Harach et al. [39] reported that the depletion of enteric bacteria in AβAPP mice (a genetic model of AD) was associated with a decrease in central Aβ protein levels, and the subsequent transplantation with microbiota from AD mice enhanced the amyloid burden in the brain, thus suggesting that alterations of enteric bacteria in AD contribute to the accumulation of Aβ protein in the CNS. However, these authors did not evaluate whether, besides alterations of enteric bacteria and increased enteric AβPP expression, AD animals were characterized by intestinal Aβ and p-Tau accumulation and/or enteric neurogenic/inflammatory responses that could contribute to CNS pathology. In this regard, it has been reported that TgCRND8 mice (a genetic model of AD) displayed an increased enteric Aβ protein expression, activation of intestinal inflammatory pathways, neuronal loss and enteric glial activation in the early stages of the disease before the onset of neuroinflammation in the CNS, thus supporting the view that intestinal Aβ protein accumulation and enteric neurogenic/inflammatory responses represent one of the earliest events in AD [86]. In addition, two recent studies reported that APP/PS1 mice displayed an increased enteric Aβ and p-Tau protein expression, intestinal immune/inflammatory cell activation and rearrangements of enteric neuronal coding, characterized by a decrease in neuronal nitric oxide synthase (nNOS) and choline acetyltransferase (ChAT), thus supporting the hypothesis that, in AD, intestinal Aβ and p-Tau protein accumulation could shape enteric and peripheral neurogenic/inflammatory responses and contribute to neuroinflammation and neurodegeneration in the CNS [28, 38].

Overall, current data from human and pre-clinical studies allow to hypothesize that changes in gut microbiota and the Aβ and p-Tau protein accumulation in intestinal tissues promote enteric neurogenic/inflammatory responses and contribute to CNS pathology. However, current evidence does not allow to establish a causal relationship between gut dysbiosis, intestinal Aβ and p-Tau accumulation, enteric inflammation and AD pathology. In addition, there is a lack of data on possible morphofunctional alterations of intestinal epithelial barrier in AD, which could contribute to bacterial translocation into the lamina propria with consequent activation of immune/inflammatory pathways. Therefore, extensive investigations based on integrated/holistic approaches, are awaited for understanding the relationship between gut dysbiosis, intestinal Aβ and p-Tau protein accumulation and enteric neurogenic/inflammatory responses in the early stages of AD, as well as for clarifying how such alterations could contribute to neuroinflammation and neurodegeneration in the CNS.

## Amyotrophic lateral sclerosis

ALS patients experience GI symptoms including dysphagia, delayed gastric emptying and impaired colonic transit [62, 95]. However, unlike the other neurological disorders, human and preclinical evidence about the role of enteric bacteria-neuro-immune network in the pathophysiology of ALS and related GI dysfunctions is scanty.

At present, only one clinical study has reported that ALS patients are characterized by changes in enteric bacteria composition. In particular, ALS patients display a significant decrease in Firmicutes/Bacteroidetes ratio along with a reduced relative abundance of *Oscillibacter*, *Anaerostipes* and Lachnospiraceae, thus suggesting a pro-inflammatory dysbiosis that could compromise the intestinal epithelial barrier and promote immune/inflammatory responses with consequent alterations of bowel motility [26]. However, the authors did not evaluate whether, besides enteric bacteria, ALS patients were characterized by alterations of intestinal epithelial barrier and/or immune/inflammatory cell activation. In this context, two pioneering pre-clinical studies, carried out in G93A animals (a genetic model of ALS), have investigated a correlation between gut dysbiosis, altered intestinal permeability and enteric inflammatory/neurogenic responses. The first study by Wu et al. [107] showed that, in ALS mice in the early stages of the disease, gut dysbiosis, characterized by a reduced abundance of *Butyrivibrio fibrisolvens, Escherichia coli* and Firmicutes, correlated with a decreased tight and adherens junction protein expression (ZO-1 and e-cadherin, respectively) and an increased in vivo intestinal permeability. In addition, ALS mice displayed an increase in the number of abnormal Paneth cells and pro-inflammatory IL-17 cytokine levels both in intestinal tissues and blood [107]. Likewise, Zhang et al. [115] reported a correlation between gut dysbiosis and morphofunctional

alterations of intestinal permeability in G93A animals, since the earliest stages of the disease. Moreover, they observed that, following treatment with butyrate, G93A mice displayed a restored gut microbiota homeostasis and intestinal epithelial barrier integrity, as well as an improvement of central and peripheral symptoms of the disease [115].

Current pre-clinical findings suggest that changes in gut microbiota, impaired intestinal permeability and enteric inflammation represent one of the earliest events in ALS, and that the treatments with SCFAs can restore the intestinal homeostasis and counteract the progression of the disease. However, these pioneristic findings do not allow to firmly establish whether the alterations of the enteric bacteria-neuro-immune network contribute to the pathophysiology of ALS, or whether they occur as a consequence of the central neurodegenerative processes. Therefore, further investigations should be implemented to better clarify the role of enteric bacteria-neuro-immune network in animal models as well as in ALS patients, since the earlier stages of the disease.

## Multiple sclerosis

Chronic constipation or fecal incontinence represent the main bowel disturbances in patients with MS. Such disorders may occur both in the early and advanced stages of the disease, with a prevalence ranging from 60 to 70% [102]. In this context, several research efforts are currently being focused on unraveling the role of enteric bacteria-neuro-immune network in the pathogenesis of MS and related bowel disturbances.

Current evidence indicates that MS patients are characterized by relevant changes in enteric bacteria composition. In particular, MS and relapsing–remitting MS (RRMS) patients display a significant decrease in the percentage of several *Bacteroides*, including *Bacteroides stercoris*, *Bacteroides coprocola*, and *Bacteroides coprophilus,* along with an increased relative abundance of the *Pseudomonas, Mycoplana, Haemophilus, Blautia* and *Dorea* genera, thus suggesting a pro-inflammatory dysbiosis that could compromise the intestinal epithelial barrier and facilitate immune/inflammatory responses with consequent alterations of bowel motility [14, 61]. In support of this view, alterations of intestinal permeability and signs of systemic inflammation have been documented in MS patients, and these patterns appear to be correlated with the disability status of the disease [11]. In addition, a recent paper by Wunsch et al. [108] reported ENS nerve fiber disintegration and EGC activation in two of three MS patients. However, despite these interesting observations, it remains unclear whether gut dysbiosis, altered intestinal permeability and immune/inflammatory responses contribute to neuroinflammation and neurodegeneration in the CNS, or whether they occur as a consequence of the initiation of the central neurodegenerative process. In this context, pioneering evidence, showing the relevance of enteric bacteria-neuro-immune network in the pathophysiology of MS, comes from pre-clinical studies on animals with experimental autoimmune encephalomyelitis (EAE), a murine model that reproduces many of the features of MS [93]. In a previous study, Yokote et al. [110] observed that the pharmacological modulation of gut microbiota with an antibiotic cocktail in mice, 1 week before EAE induction, slowed down the development of the disease. Lee et al. [53] observed that antibiotic administration to EAE mice reduced the systemic pro-inflammatory cytokine levels, decreased the number of mesenteric Th17 pro-inflammatory cells and attenuated the severity of the disease. Conversely, EAE GF animals, harboring pathogenic segmented filamentous bacteria, displayed an increase in pro-inflammatory IL-17A-producing CD4 + T cells both in the gut and CNS, and a greater disease severity [53]. In addition, two recent studies reported that treatment with a SCFA mixture or probiotics to EAE mice increased the density of anti-inflammatory Treg cells and reduced inflammatory cell infiltration and demyelination in the CNS [37, 51]. These findings suggest that changes in gut microbiota may contribute to MS pathology, and that treatment with antibiotics, SCFAs or probiotics might counteract peripheral and central inflammation as well as the CNS demyelination process. However, the authors did not evaluate whether, besides enteric bacteria, alterations of intestinal epithelial barrier and enteric inflammatory/neurogenic responses could contribute to CNS pathology and related intestinal symptoms. In this regard, it has been reported that EAE mice displayed an abnormal intestinal permeability, an increased infiltration of Th1/Th17 pro-inflammatory cells and a decreased number of Treg cells in the early stages of the disease, before the onset of neurological symptoms and the phase of paralysis [65]. Moreover, Wunsch et al. [108] observed that EAE animals displayed enteric glial activation, neuronal loss and abnormal GI motility before the onset of CNS lesions and neurological deficiencies. These findings represent a major point of novelty, since they support the view that abnormal intestinal permeability, neurogenic/inflammatory cell activation and altered intestinal motility may represent one of the earliest steps of MS, preceding the onset of neurological and peripheral symptoms.

Taken together, current data from human and pre-clinical studies expand further the available knowledge about the role of enteric bacteria-neuro-immune network in the pathophysiology of MS. Indeed, it appears that changes in gut microbiota composition, abnormal intestinal permeability and enteric inflammation in the early stages of the disease, besides determining intestinal motor dysfunctions, could promote a condition of peripheral inflammation and contribute to neuroinflammation and neurodegeneration in the

CNS. However, current evidence does not allow to establish a causal relationship between gut dysbiosis, altered intestinal permeability, enteric inflammation and MS pathology. In this respect, some important issues remain to be addressed. For instance, even though it is well acknowledged that intestinal dysbiosis can compromise intestinal epithelial barrier, it is not clear, in the setting of MS, what specific alterations of enteric bacteria could contribute to alter the intestinal permeability. In addition, it remains to be established what are the mechanisms through which gut microbiota induce innate and adaptive immune responses in the early stages of MS. To clarify these points, research efforts should be dedicated to elucidate the role of enteric bacteria-neuro-immune network in MS and related intestinal symptoms both in EAE animals and MS patients, since the earliest stages of the disease.

## Conclusions and future perspectives

Current data from human studies suggest that gut dysbiosis and enteric inflammation might represent a common path to neurodegerative diseases. Indeed, even though each disease displays distinct clinical, neuropathological and genetic features, patients with PD, AD and MS are characterized by significant changes in gut microbiota composition and signs of enteric inflammation since the earliest stages of the disease. Besides the induction of bowel motor dysfunctions, these changes could promote conditions of chronic peripheral inflammation and contribute to neuroinflammation and neurodegeneration in the CNS. In support of this view, alterations of intestinal bacteria and enteric neurogenic/inflammatory responses in PD, AD and MS patients have been found to correlate with the severity of the disease. In addition, PD and MS patients display an altered intestinal permeability that seems to contribute to the onset of enteric inflammation. However, human studies do not allow to establish a causal and mutual relationship between gut dysbiosis, altered intestinal permeability and enteric inflammation. Moreover, it remains unclear whether alterations of the enteric bacteria-neuro-immune network precede, follow or both the occurrence of central neurodegeneration. In this regard, the development of experimental models of neurodegenerative diseases, including PD, AD, MS and ALS, has allowed to better understand the pathophysiological role of enteric bacteria-neuro-immune network in the onset of central neurodegeneration. Indeed, even though each experimental model displays distinct pathophysiological features for each disease, gut dysbiosis, altered intestinal permeability and enteric neurogenic/inflammatory responses occur as early events in PD, AD, MS and ALS. Moreover, these processes, besides determining intestinal dysfunctions, appear to contribute to neuroinflammation and neurodegeneration in the CNS. In support of this view, the pharmacological manipulation or target-depletion of gut microbiota in PD, AD, MS and ALS animals has been found to counteract the progression of central neurodegeneration as well as intestinal and peripheral symptoms.

Based on the above considerations and pooling together the available pre-clinical and human evidence from literature, it is conceivable that, in the very early stages of the disease, patients with neurological disorders are characterized by abnormal interactions among gut microbiota, intestinal barrier and the enteric neuro-immune system, leading to enteric inflammatory activation. In the subsequent stages of the disease, the enteric/immune inflammatory activation likely triggers events of inflammation and neurodegeneration in the CNS through the gut–brain ascending pathways. In this setting, central neuroinflammation and subsequent neurodegeneration could contribute to exacerbate enteric neuroimmune/inflammatory responses, via brain-gut descending pathways, thus generating a sort of positive loop that could drive the chronicization of the ongoing central and peripheral neuroinflammatory and neurodegenerative processes. However, the molecular mechanisms underlying the alterations of enteric bacteria-neuro-immune network in neurological disorders as well as its role in the pathophysiology of central neurodegeneration remain poorly understood.

Considerable gaps in our knowledge concern whether gender, the genetic background and/or environmental factors, such as diet, could influence the interactions among gut microbiota, intestinal barrier and the enteric neuroimmune system both under physiological conditions and in the presence of neurological disorders. For instance, despite consistent evidence that males and females display gender-specific differences in the immune system and gut microbiota composition [40, 112], and that gender differences are prominent in neurological disorders, including PD, AD, ALS and MS [113], the influence of gender in the enteric bacteria-neuro-immune interplay remains fairly unclear. In addition, there is a lack of data about possible relationships among gender, enteric bacteria-neuro-immune network and CNS pathology.

Increasing evidence supports associations of the human genetic background with enteric bacteria, immune/inflammatory responses and neurological disorders [24]. For instance, genetic variants, linked to familial and sporadic PD, were found to shape gut immune/inflammatory responses [24]. However, knowledge of data about the possible influence of the genetic variants associated with PD, AD and MS on the abnormal interactions among gut microbiota, intestinal mucosal barrier and enteric neuroimmune system is lacking. As far as environmental factors are concerned, several lines of evidence support the contention that diet can change the composition of gut microbiota, with consequent alterations of intestinal permeability and immune/inflammatory cell activation that,

in turn, could trigger events of inflammation and neurodegeneration in the CNS through the gut–brain ascending pathways [71, 73, 79]. However, an integrated view about the impact of diet in the alterations of enteric bacteria-neuro-immune network, gut dysfunctions and the main neurological diseases, including PD, AD, ALS and MS, is missing and requires investigations.

In conclusion, based on current knowledge, some important issues remain to be addressed: (1) what is the actual role of intestinal epithelial barrier in the enteric immune/inflammatory activation in the early stages of neurodegenerative diseases? (2) Does it represent the crossroad between changes in gut microbiota and enteric/immune inflammatory activation? (3) how can intestinal immune/inflammatory cell activation trigger events of neuroinflammation and neurodegeneration in the CNS? (4) What is the role of bacteria-neuro-immune gut–brain axis in the onset of neuroinflammation and neurodegeneration in the CNS? (5) Can the alterations of enteric bacteria-neuro-immune network represent an early biomarker of the main neurodegenerative diseases? (6) Can the pharmacological targeting of enteric microbiota, intestinal mucosal barrier and/or enteric immune system confer any benefit on central neurodegenerative diseases, in terms of prevention, cure or maintenance of remission? (7) What is the relationship among gender, gut microbiota, intestinal mucosal barrier and enteric neuro-immune system interplay and neurodegenerative disorders? (8) Can the genetic background of PD, AD and MS patients influence the gut microbiota, intestinal mucosal barrier and enteric neuro-immune system interplay? (9) What is the impact of environmental factors, such as diet, in the alterations of enteric-bacteria-neuro-immune network, gut dysfunctions and neurodegenerative diseases? To clarify these points, research efforts should be addressed to investigate, by means of holistic approaches, the alterations of gut microbiota, intestinal epithelial barrier and enteric neuro-immune system interplay both in genetic and toxin-induced animal models since the earliest stages of disease. In addition, translational studies on male and female patients at very early stages of the diseases as well as in subjects with GI dysfunctions and genetic susceptibility to develop neurodegenerative diseases should be implemented. Unraveling these aspects could pave the way to a Copernican revolution for both the prevention and clinical management of main neurological disorders and related intestinal dysfunctions.

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## Compliance with ethical standards

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