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Review Article

The Gut–brain–immune Triad in Neurodegeneration: An Integrated Perspective

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Abstract

Neurodegenerative diseases (NDs) represent a major global health challenge in aging populations, with their incidence continuing to rise worldwide. Although substantial progress has been made in elucidating the clinical features and molecular underpinnings of these disorders, the precise mechanisms driving neurodegeneration remain incompletely understood. This review examines the increasing significance of the gut–brain–immune triad in the pathogenesis of NDs, with particular attention to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. It explores how disruptions in gut microbiota composition and function influence neuroinflammation, blood–brain barrier integrity, and immune modulation through microbial-derived metabolites, including short-chain fatty acids, lipopolysaccharides, and bacterial amyloids. In both Alzheimer's and Parkinson's diseases, a reduced abundance of short-chain fatty acid-producing bacterial taxa has been consistently associated with heightened pro-inflammatory signaling, thereby facilitating disease progression. Although detailed mechanistic understanding remains limited, experimental evidence—primarily from rodent models—indicates that microbial metabolites derived from a dysbiotic gut may initiate or aggravate central nervous system dysfunctions, such as neuroinflammation, synaptic dysregulation, neuronal degeneration, and disruptions in neurotransmitter signaling via vagal, humoral, and immune-mediated pathways. The review further highlights how gut microbiota alterations in amyotrophic lateral sclerosis and multiple sclerosis contribute to dysregulated T cell polarization, glial cell activation, and central nervous system inflammation, implicating microbial factors in disease pathophysiology. In addition to identifying critical knowledge gaps, the review emphasizes the need for sustained, multifactorial research efforts, including the development of physiologically relevant brain–gut organoid models and the implementation of standardized experimental protocols. A major limitation in the field remains the difficulty of establishing causality, as clinical manifestations often arise after extended preclinical phases—lasting years or decades—during which aging, dietary patterns, pharmacological exposures, environmental factors, and comorbidities collectively modulate the gut microbiome. Finally, the review discusses how microbial influences on host epigenetic regulation may offer innovative avenues for modulating neuroimmune dynamics, underscoring the therapeutic potential of targeted microbiome-based interventions in neurodegenerative diseases.

Introduction

As the worldwide population continues to age rapidly, neurodegenerative diseases (NDs) have become a prominent cause of disability and death among senior citizens.[1,2] From 1990 to 2021, there was an 18.2% rise (95% uncertainty interval: 8.7–26.7) in global disability-adjusted life years due to neurological disorders, now impacting over 40% of the global population. In 2021, Alzheimer's disease (AD) and other forms of dementia were identified as the second leading cause of disability-adjusted life years for those aged 60–79, while Parkinson's disease (PD) ranked third for individuals aged 80 and older. Together, NDs, such as AD, PD, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration, and Huntington's disease, represent a major public health issue globally.[3–6] This rising socioeconomic burden underscores the urgency to explore non-neuronal mechanisms, like the gut–brain–immune triad. These conditions lead to progressive deterioration in cognitive and motor abilities, resulting in diminished independence in daily activities and, ultimately, early death. Estimates from the

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World Alzheimer Report (2015) and similar analyses suggest that the total costs associated with dementia care may reach $9.12 trillion by 2050, representing a tenfold increase compared to 2015.[6,7] This estimate includes not only direct healthcare costs but also the wider economic consequences of lost productivity and informal caregiving. In the U.S. specifically, PD was responsible for an economic burden of $52 billion in 2017, comprising $25.4 billion in direct medical expenses and $26.5 billion in indirect costs.[8] These numbers are anticipated to increase significantly by 2040, with the global prevalence of PD expected to double.

With the rising prevalence of NDs, the associated socioeconomic burden, and the limited efficacy of neuron-centric therapies, it is increasingly important to approach neurodegeneration from a systems biology perspective. The rationale for this review is to provide a unified perspective that not only contextualizes recent discoveries but also emphasizes the translational potential of microbiome-informed and immunomodulatory interventions for preventing or modifying the trajectory of NDs.

Toward a systems biology framework for NDs

Despite increasing awareness and economic challenges, the neuron-focused perspective has led to an inadequate understanding of NDs. Recent studies have begun to show that neurodegeneration might also be caused by interactions throughout the body, including factors from the immune system and signals from the gut.[9–12] Research has historically concentrated on mechanisms within neurons, such as protein misfolding, defects in synaptic transmission, mitochondrial dysfunction, and oxidative stress.[13–16] While biological processes are important, they do not fully explain the variability associated with NDs. In fact, there is a growing appreciation of non-neuronal mechanisms, including glial dysfunction, chronic neuroinflammation related to microglial or immune dysregulation, and metabolic dysfunctions.[16–19] These processes are critical to the initiation and progression of NDs as we shift toward a more integrated conceptualization of the brain as a dynamic, bidirectional network with the immune system and gut microbiome. Moving away from a neuron-centric view to a systems biology view of disease may lead to the identification of new therapeutic targets and explain why neuron-focused interventions alone fail to halt disease progression.

Gut microbiota as a neuroregulatory hub

The human microbiome comprises a complex and ever-changing collection of various microbial communities found in specific anatomical areas throughout the body.[20,21] Through coevolution, these microbial ecosystems have developed essential roles in regulating host physiology and play a significant part in maintaining overall health.[22,23] Disruptions in the composition or function of these communities, especially in the gut, are increasingly linked to the origins and progression of numerous diseases, particularly NDs.[9–12,24] Among the various microbial communities present in the body, the gut microbiota has garnered significant attention for its diverse roles in regulating immune balance, influencing brain development in early life, and affecting cognitive behavior and overall brain health throughout an individual's lifetime.[25–27] Referred to as the "second genome" or "second brain", the gut microbiome regulates neuroregulation by producing soluble neuroactive metabolites derived from food, modulating immune responses, and communicating with the central nervous system (CNS) through the vagus nerve.[28–30]

Consequently, neuroinflammation, previously thought to be merely a bystander effect or a consequence rather than a cause of neurodegeneration, is now increasingly understood as a key driver of disease progression.[18,19] Essentially, this approach supports a more unified conceptual framework for understanding NDs through the gut–brain–immune triad, where signals from gut microbiota, immune cell activity, and CNS functioning are deeply interconnected.[31,32] In essence, this triad model allows for a broad representation of neurodegeneration, capturing multifactorial aspects that reductionist viewpoints often ignore. It provides an integrated perspective to reconceptualize longstanding questions in NDs and inspire new therapeutic approaches. In this context, Figure 1 provides a visual representation of the gut–brain–immune triad as a central element in the pathogenesis of NDs.

Microbial signals and gaps in ND research

Critically, this review aims to address gaps in the current literature that impede a comprehensive understanding of NDs. A key deficiency lies in the limited incorporation of epigenetic regulators—particularly microRNAs (miRNAs), which are modulated by microbial metabolites and immune signals—into prevailing pathophysiological models of NDs.[33,34] Despite their established roles in regulating neuroimmune gene expression, synaptic plasticity, and neuronal resilience, miRNAs remain underrepresented in integrative frameworks of disease progression.[35,36] Another underexplored area is the concept of trained immunity, defined as the long-term functional reprogramming of innate immune cells following microbial or inflammatory exposures.[37,38] Trained immunity may represent a critical mechanism through which early-life or chronic gut dysbiosis primes the CNS for heightened susceptibility to neuroinflammatory insults and neurodegeneration later in life.[39,40] Moreover, the field is hindered by a lack of standardized methodologies, particularly in microbiome sampling protocols, metadata curation, and the development of translational models that accurately replicate human ND pathophysiology. These limitations restrict reproducibility, impede cross-study comparisons, and delay clinical translation .[41,42]

Structure of the review article

In light of these persistent challenges, this review advocates for a fundamental reorientation of both preclinical and clinical research approaches within the field, promoting a systems-level perspective that transcends traditional neuron-centric paradigms. Emerging technologies, such as brain–gut organoid platforms, integrative multi-omics analyses, and large-scale longitudinal cohort studies, provide promising avenues for elucidating the dynamic and context-dependent interactions among the gut microbiome, immune system, and CNS throughout the human lifespan.[43–45] Ultimately, this review proposes a more comprehensive and mechanistically informed framework for understanding NDs through the lens of the gut–brain–immune triad. By emphasizing the roles of epigenetic and metabolic reprogramming, it highlights previously overlooked drivers of disease and identifies novel therapeutic targets at the microbiota–immune interface. These insights establish a foundation for the development of innovative, microbiome-informed interventions aimed at preventing or modifying the trajectory of NDs.

Importantly, to develop a broad and integrated perspective for this review, a comprehensive literature search was conducted across major academic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search targeted experimental (i.e., *in vitro* and *in vivo*) and clinical studies pertinent to the central themes of the review. A focused, keyword-driven search strategy was employed to ensure alignment with the overarching research questions. Priority was given to articles published within

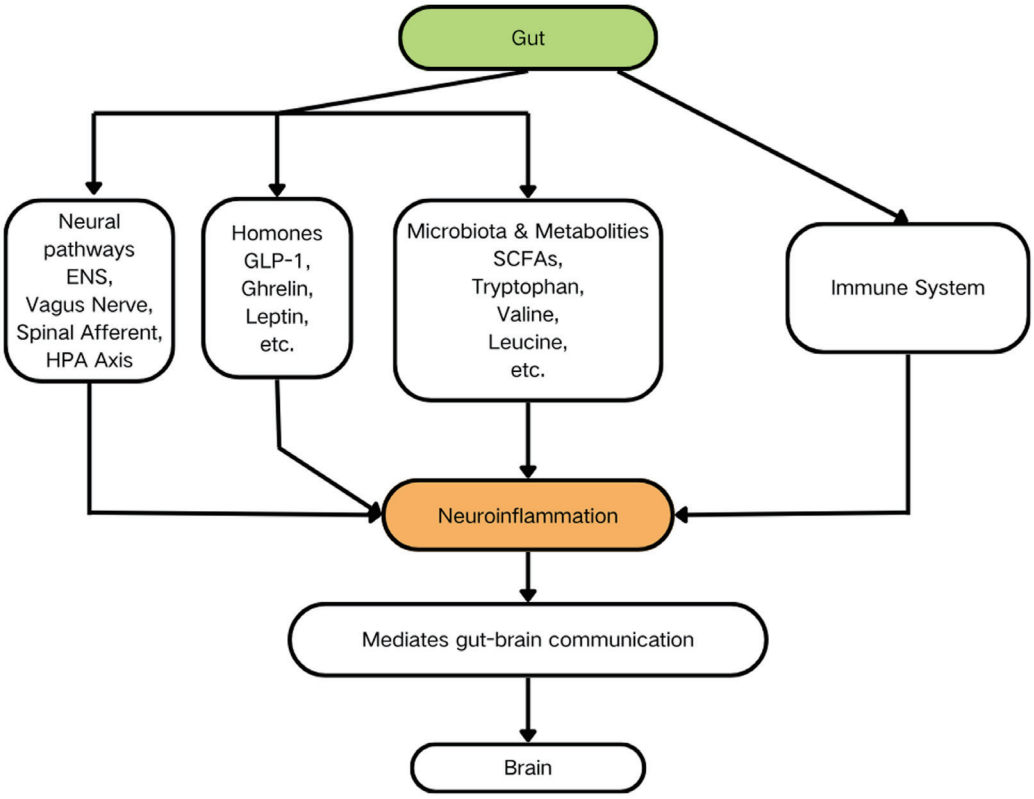

Fig. 1. The gut–brain–immune triad: A key component in the pathogenesis of neurodegenerative diseases. This schematic illustrates the central role of the gut–brain–immune axis in the pathogenesis of neurodegenerative diseases (NDs), positioning the gut (green) as the origin of various signaling cascades that influence immune responses and brain function. Gut dysbiosis, characterized by a reduction in short-chain fatty acid (SCFA)-producing bacteria and an increase in pro-inflammatory components such as lipopolysaccharide (LPS), disrupts neural (enteric nervous system, vagus nerve, spinal afferents, hypothalamic–pituitary–adrenal axis), hormonal (glucagon-like peptide-1, ghrelin, leptin), and microbial metabolic pathways (SCFAs, tryptophan, valine, leucine), all of which are shown in white boxes. These interconnected signals converge on neuroinflammation (yellow), depicted as the central integrative hub linking peripheral disturbances to central nervous system (CNS) dysfunction. Dysbiosis-induced immune activation promotes systemic inflammation, T cell imbalance, and the infiltration of immune cells into the CNS, resulting in microglial activation, cytokine release, synaptic disruption, and neuronal injury. While not explicitly illustrated, neural cells such as neurons, astrocytes, and oligodendrocytes are primary targets of this inflammatory cascade. Additionally, vagal transmission of microbial cues and SCFA-mediated epigenetic modifications in both immune and neural cells contribute to sustained neuroinflammation. The communication is bidirectional, with CNS pathology feeding back to alter gut physiology and microbiota composition, forming a self-perpetuating pathological loop. The brain (white) represents the final recipient of these signals. Overall, the figure highlights the gut as a central regulatory node and neuroinflammation as a key therapeutic target within the gut–brain–immune triad in NDs. ENS, enteric nervous system; GLP-1, glucagon-like peptide-1; HPA, hypothalamic–pituitary–adrenal.

the past five years, with the cutoff date set to August 2025, corresponding to the period of manuscript preparation.

Communication pathways in the gut–brain–immune triad

As previously mentioned, the two-way communication between the gut microbiota, immune system, and CNS establishes the foundation of the gut–brain–immune axis. This interactive triad engages through various interconnected pathways, including neural pathways (via the vagus nerve and the enteric nervous system (ENS)), endocrine signals (hormones secreted by enteroendocrine cells), immune responses (cytokine signaling), and metabolic processes (microbial metabolites such as short-chain fatty acids (SCFAs)).[46–48] Gut microbes can affect brain activity, immune function, and neuroinflammation through these routes. Dysregulations in this system have increasingly been associated with the onset of NDs, emphasizing the microbiome as an essential and modifiable factor in the progression of these diseases.[30–32] The subsequent sections will delve into these mechanisms in greater depth.

Gut–CNS communication

The gastrointestinal (GI) system communicates with the CNS through various pathways of neural transmission, microbial byproducts, immune signals like cytokines, and hormonal channels.[49,50] Central to this complex system is the vagus nerve, which serves as the primary two-way pathway, transmitting sensory information from the stomach and intestines to the brainstem while also regulating GI functions and systemic inflammation via the cholinergic anti-inflammatory reflex.[51,52] The ENS, often referred to as the "second brain", is made up of a vast network of intrinsic neurons that independently manage GI motility, secretion, and the integrity of the intestinal barrier.[53,54] The ENS is also linked to the CNS through sympathetic and parasympathetic fibers. Gut microbiota influence neurocircuitry through the production of bioactive metabolites such as SCFAs,

with particular emphasis on butyrate. SCFAs like butyrate can modulate gene expression via epigenetic mechanisms and immunomodulatory effects.[55,56] Specifically, butyrate functions as a histone deacetylase inhibitor, enhancing chromatin accessibility in microglia and promoting their polarization from a pro-inflammatory M1 state to an anti-inflammatory M2 phenotype through the interleukin (IL)-4/IL-13–STAT6 signaling pathway, thereby supporting neuroimmune balance and maintaining CNS homeostasis.[57–60] Furthermore, catabolites derived from tryptophan affect the serotonergic and kynurenine pathways, which are crucial for maintaining neuroimmune balance.[61,62] Specific bacterial species can produce neurotransmitter precursors such as gamma-aminobutyric acid, serotonin, and dopamine, which may interact with enteric neurons and vagal afferent fibers, thereby altering neuronal excitability and neurobehavioral characteristics.[63,64] Intestinal epithelial enteroendocrine cells also function as sensors for luminal substances and microbial signals. They release systemic hormones like glucagon-like peptide (GLP)-1, peptide YY, cholecystokinin, and ghrelin, which can reach the brain or connect to hypothalamic and limbic systems through vagal afferents, transmitting signals related to metabolism, stress, and cognition.[65–67] Collectively, these interconnected pathways form a dynamic interface between the gut and the brain, known as the gut–brain axis (GBA), where microbial, neuronal, and hormonal signals interplay to influence CNS activity, neuroinflammation, and, subsequently, the likelihood of NDs.

Gut–immune system crosstalk

The gut microbiota is essential for the immune system's development and regulation, significantly influencing NDs. Host–microbe interactions initiate when pattern recognition receptors present on intestinal epithelial cells and innate immune cells detect microbial-associated molecular patterns like lipopolysaccharides (LPS) and peptidoglycans.[68,69] This interaction helps maintain immune balance by harmonizing pro-inflammatory signals with regulatory pathways. Changes in microbial composition, referred to as dysbiosis, can undermine the structural integrity of the gut epithelium by modifying the expression of tight junction proteins.[70,71] This change results in increased intestinal permeability, often termed "leaky gut". Consequently, microbial antigens and metabolites can infiltrate the lamina propria and enter systemic circulation, initiating antigen presentation, T cell polarization, and widespread inflammatory responses that can influence the CNS.[72,73] At the core of mucosal defense is the gut-associated lymphoid tissue, which oversees immunological surveillance and tolerance through pattern recognition receptor signaling and the activation of nuclear factor kappa-B (NF-κB).[74] Simultaneously, microbial metabolites, particularly SCFAs and compounds derived from tryptophan, serve immunoregulatory functions, affecting dendritic cell maturation, regulatory T cell (Treg) induction, and T helper 17 (Th17) cell differentiation. These mechanisms adjust key cytokines such as IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α), influencing peripheral immune responses and neuroimmune interactions, including microglial activation within the brain.[75,76] Furthermore, this immunological network is intricately connected to the hypothalamic–pituitary–adrenal axis, which acts as the body's primary stress response mechanism.[77] Signals derived from the microbiota, transmitted via vagal afferents or immune pathways, can stimulate the hypothalamus to release corticotropin-releasing hormone.[78,79] This, in turn, causes the pituitary gland to release adrenocorticotropic hormone, prompting the adrenal glands to produce glucocorticoids such as cortisol. These hormones create feedback loops that influence immune activity and microbial ecology, establishing a reciprocal neuroimmune feedback system.[80,81] Long-term disruptions in this loop, such as consistently elevated cortisol levels, may heighten blood–brain barrier (BBB) permeability, maintain neuroinflammation, and hasten the progression of NDs.[82,83]

Immune–CNS interface: A key node in the gut–brain–immune triad

In the gut–brain–immune triad, the reciprocal communication between the immune system and the CNS is essential for preserving brain equilibrium and influencing vulnerability to NDs. This communication occurs through a complex network of signaling molecules, immune cells, and microbial metabolites that together influence neural functions, glial activities, and neuroinflammation.[84,85] Cytokine signaling serves as a primary means of immune interaction with the CNS. Proinflammatory cytokines such as IL-6, TNF-α, and IL-1 can penetrate the BBB or act on certain areas of the CNS that have a more permeable barrier.[86,87] For example, pro-inflammatory cytokines like IL-1 are particularly effective in perturbing CNS homeostasis. They affect BBB permeability by compromising the structure of capillary endothelial tight junctions and stimulate downstream pro-inflammatory pathways while simultaneously reducing the protective role of astrocytes by limiting their production of sonic hedgehog, another crucial factor for maintaining BBB homeostasis.[88,89] Furthermore, IL-1 prompts astrocytes to secrete potentially neurotoxic substances that enhance localized inflammation, foster angiogenesis, and elevate vascular permeability.[90,91] Together, these processes trigger and maintain BBB dysfunction, fostering a pro-inflammatory environment within the CNS that may further lead to neurodegeneration. Additionally, the movement of immune cells through a disrupted BBB exacerbates neural damage. Peripheral immune cells, including activated monocytes and T lymphocytes—often primed by microbial antigens and cytokine-rich environments in the gut—can migrate into the CNS. Once they enter the CNS, these peripheral immune cells may interact with resident glial cells, leading to chronic inflammation and neuronal impairment.[92,93] Microglia, the inherent immune guardians of the CNS, serve as another crucial point of interaction within this triad.[94] Microglia play a vital role in immune monitoring, synaptic pruning, and injury response.[95,96] Notably, germ-free (GF) mice exhibit significant pathological issues in microglia, including unusual shapes, hindered maturation, and metabolic disorders.[97,98] The abnormalities in microglia found in GF animals are mainly linked to the lack of SCFAs, especially acetate, which is crucial. Acetate reprograms microglia during resting metabolic phases, and it has been demonstrated to restore normal maturation and functional responses in GF models, further supporting the idea that metabolites derived from the gut are integral in regulating the immune tone of the CNS.[99–101]

To summarize, the interaction between the immune system and the CNS is crucial and dynamic in the context of the gut–brain–immune triad. Proinflammatory substances, such as IL-1, can disrupt the BBB and worsen glial dysfunction and neuronal susceptibility. At the same time, microbial metabolites like acetate provide immunomodulatory signals that contribute to the maintenance of immune homeostasis in the CNS. Gaining insight into the intricacies of this two-way communication establishes a significant conceptual basis for developing therapeutic approaches aimed at modifying peripheral immunity while safeguarding CNS health in NDs.

Dysregulation of the gut–brain–immune axis in NDs

AD

AD represents the most prevalent type of dementia in older adults, marked by a gradual loss of neurons and cognitive deterioration that primarily impacts the CNS. Notable pathological characteristics include the buildup of amyloid β (Aβ) plaques outside cells and the accumulation of hyperphosphorylated Tau protein within neuronal axons and dendrites.[102–104] Despite extensive research over many years, the exact mechanisms responsible for AD are still not fully comprehended. Recent studies are increasingly highlighting the role of gut microbiota in the onset of AD.[105–107] Many patients display gut dysbiosis, an alteration in gut microflora characterized by a reduction in beneficial anti-inflammatory bacteria and an increase in harmful pro-inflammatory species.[108,109] This microbial imbalance gives rise to the production of detrimental metabolites that hinder protective microbes, leading to systemic and neuroinflammation and accelerating NDs.[110,111] Gut dysbiosis may affect amyloidogenic pathways through multiple mechanisms. Microbial components like bacterial amyloids and LPS can stimulate the host immune response, resulting in an overproduction of endogenous Aβ peptides. These microbial elements also facilitate Aβ aggregation and obstruct its clearance, thus promoting plaque formation in the brain. Furthermore, immune activation driven by dysbiosis amplifies the reactivity of microglia—the immune cells native to the CNS—perpetuating a long-lasting pro-inflammatory environment.[112–114] Inflammation originating from the gut can compromise the BBB, allowing microbial products and inflammatory mediators to infiltrate the CNS and further activate microglia. Continuous microglial activation worsens Aβ and Tau pathology, disrupts synaptic functionality, and leads to ongoing neuronal loss, creating a self-reinforcing cycle of neuroinflammation and degeneration.[115–117] Among the microbial agents linked to this condition, LPS, a potent endotoxin from Gram-negative bacteria, plays a particularly crucial role. Increased levels of LPS have been observed in the blood and brains of individuals with AD.[118,119] LPS undermines the integrity of the BBB and directly activates CNS immune pathways by binding to toll-like receptor 4 on microglia and astrocytes. This action triggers the NF-κB signaling pathway and encourages the release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. These cytokines further disrupt neuronal function, promote Tau hyperphosphorylation, and hinder microglial phagocytosis of Aβ, thereby exacerbating AD pathology.[120–122]

One significant way that gut dysbiosis influences the brain is by altering gut microbial metabolites, especially SCFAs. There is growing evidence that changes in SCFA levels and a decrease in SCFA-producing bacteria are linked to the development and progression of NDs, such as AD.[123–125] Beneficial gut bacteria, including *Faecalibacterium prausnitzi*i, *Roseburia spp*., and *Bacteroides spp*., generate SCFAs like acetate, propionate, and butyrate during the fermentation of dietary fibers.[126,127] These metabolites are vital for intestinal health and exhibit systemic effects that are essential for brain function and immune regulation. In states of neuroinflammation, SCFAs engage with G-protein-coupled receptors (like GPR41, GPR43, and GPR109A) found on immune and epithelial cells. This engagement contributes to diminishing pro-inflammatory signals and curtailing the release of cytokines, including TNF-α, IL-6, and IL-1β, which are frequently elevated in cases of AD.[128,129] Research has demonstrated that administering acetate can reduce LPS-induced glial activation, lower brain levels of IL-1β, and enhance levels of acetyl coenzyme A and acetylated histones.[130,131] Additionally, SCFAs help alleviate inflammation in the hippocampus and neuronal damage triggered by a diet high in fructose by restoring the integrity of the intestinal epithelial barrier and addressing challenges related to the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 6 inflammasome.[132,133] SCFAs are also crucial for preserving the integrity of the BBB, which is often impaired in AD. For example, sodium butyrate boosts the expression of tight junction proteins, including claudin-5, occludin, and zonula occludens-1, within brain endothelial cells, thus improving the structure and functionality of the BBB.[134,135] Research conducted in GF mice has indicated a significant increase in BBB permeability, a condition that is mitigated when these mice are colonized with SCFA-producing microbiota like *Clostridium tyrobutyricum*. This restoration correlates with an uptick in the expression of tight junction proteins and enhanced integrity of the BBB.[136,137]

The combined results highlight the important function of SCFAs in influencing neuroimmune interactions and preserving homeostasis in the CNS. Therefore, alterations in SCFA production or the composition of gut microbes could play a key role in the chronic inflammation, barrier dysfunction, and ongoing neurodegeneration associated with AD.

PD

After AD, PD emerges as the most common ND and is rapidly becoming more prevalent worldwide. Despite thorough investigation, the causes and development of PD remain insufficiently understood. A distinctive pathological characteristic of PD is the accumulation of misfolded alpha-synuclein (α-synuclein) proteins in specific areas of the brain, leading to the formation of Lewy bodies, neurodegeneration, and a gradual decline in neurological function.[138,139] Recently, the GI tract has attracted interest as a potential primary site for PD pathology, signaling a shift in perspective that revisits previously considered theories and places the disease within the framework of gut–brain–immune triad dysfunction.[140] The "gut-first" hypothesis proposes that PD starts in the GI tract, with early non-motor symptoms such as constipation and bloating often appearing up to a decade before motor symptoms develop.[141,142] Interestingly, aggregates of α-synuclein have been detected in peripheral tissues like the gut prior to CNS involvement. Research supports this hypothesis, showing that misfolded α-synuclein can transmit in a prion-like manner from the ENS to the brain via the vagus nerve.[143,144] Additionally, epidemiological studies have found a lower incidence of PD in individuals who have undergone vagotomy (the surgical severing of the vagus nerve), highlighting the importance of the GBA.[145,146]

Increasing evidence suggests that the gut microbiome significantly contributes to the development of PD by affecting neuroimmune interactions and the dynamics of α-synuclein. Numerous studies examining the microbiome have consistently found a reduction in bacteria that produce SCFAs, including *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium rectale*, in individuals diagnosed with PD.[147,148] This imbalance in microbial populations results in decreased SCFA levels, especially butyrate and propionate, which are vital for fostering intestinal immune tolerance and managing systemic inflammation by boosting the activity of Tregs and suppressing the function of antigen-presenting cells. The resulting shortfall in SCFAs likely fosters a pro-inflammatory environment that may exacerbate disease progression.[149,150] Clinically, elevated concentrations of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β have been observed in the cerebrospinal fluid and blood of individuals with PD, showing a correlation with the

severity and progression of the disease.[151,152] In the intestinal tract, biopsies from the colons of PD patients reveal heightened levels of inflammatory markers and immune cell infiltration, indicating a localized immune imbalance[153] Additionally, experimental studies show that mice overexpressing α-synuclein and colonized with microbiota from PD patients experience greater motor deficits and increased activation of microglia compared to those colonized with healthy microbiota.[154,155] In contrast, GF mice that overexpress α-synuclein exhibit lower neuroinflammation and reduced α-synuclein accumulation, highlighting the microbiota's role in promoting the disease.[156,157]

Furthermore, immune cells like intestinal macrophages and dendritic cells respond to microbial signals and host-derived antigens.[158] These immune cells subsequently activate peripheral T cells that are crucial for systemic inflammation and their ability to breach the BBB. Infiltration of $CD4^+$ and $CD8^+$ T cells in the substantia nigra has been observed in the brains of patients with PD.[159,160] Moreover, T cell responses specific to α-synuclein have been detected in the early stages of the disease, indicating a breakdown in immune tolerance.[161,162] In the CNS, activation of microglia in response to these peripheral immune signals further enhances neuroinflammation, which in turn drives the aggregation of α-synuclein and neurodegeneration.[163] These observations imply that changes in gut microbiota in PD disrupt immune equilibrium mediated by SCFAs, triggering a cascade of immune responses both peripherally and centrally that lead to the misfolding of α-synuclein within the ENS. This misfolded protein can then propagate in a prion-like manner to the brain via the vagus nerve, bolstering the gut-origin hypothesis of PD.[164,165]

Ultimately, gut dysbiosis may worsen the severity of PD by disrupting GLP-1 signaling, which is known for its anti-inflammatory and neuroprotective properties.[166,167] GLP-1 is secreted from intestinal L-cells when nutrients and microbial metabolites, like SCFAs such as acetate and butyrate produced by beneficial microbes including *Faecalibacterium prausnitzii* and *Roseburia* species, are present.[168,169] Dysbiosis leads to a decrease in SCFA production, which in turn lowers GLP-1 secretion while simultaneously increasing intestinal permeability and systemic inflammation due to elevated levels of LPS and pro-inflammatory cytokines.[170] These changes can impair GLP-1 receptor signaling and weaken its neuroprotective effects on the CNS. Importantly, GLP-1 receptor agonists (hereinafter referred to as GLP-1RAs) such as exenatide and liraglutide have shown effectiveness in preclinical models of PD by reducing dopaminergic neuron loss and α-synuclein aggregation, as well as providing clinical benefits in alleviating motor symptoms.[171,172] Together, these findings suggest that changes in GLP-1 signaling influenced by the gut microbiota may play a role in neurodegeneration associated with PD through the gut–immune–brain triad, supporting the potential therapeutic use of GLP-1-based treatments and interventions targeting the microbiome.

In summary, the disrupted gut–brain–immune connection in PD encompasses a multifaceted interaction of microbial dysbiosis, immune system activation, and neural vulnerability. This advancing insight emphasizes the GI tract as not only a key location for symptom onset but also as an important factor in the progression of PD. Consequently, it emerges as a significant target for early treatment interventions.

ALS

ALS, an ND characterized by continuous progression and selective loss of neurons, ultimately leads to muscle weakness and paralysis in affected individuals.[173] Extensive research over the years has focused on familial ALS, identifying several genetic mutations such as superoxide dismutase 1, TAR DNA-binding protein 43, and fused in sarcoma; however, over 90% of ALS cases are sporadic, suggesting that non-genetic factors like environmental elements may play a role in the disease's onset and/or progression.[174–176] One key area of interest is the human gut microbiome, which significantly affects immune regulation, metabolism, and CNS function. Changes in gut microbial communities have been observed in ALS patients, emphasizing their potential contribution to the development of the disease through the gut–immune–brain interaction.[177–179] Additionally, the rate of ALS progression is heightened with an older age of onset, suggesting that age-related shifts in host–microbiome relationships could exacerbate the disease's pathogenesis. Collectively, these insights underscore the critical need for further investigation into how signals originating from the gut contribute to immune dysfunction and neurodegeneration in ALS.

Emerging research concerning the gut–immune–brain triad in ALS indicates significant changes in gut microbiota composition, particularly affecting the Firmicutes/Bacteroidetes (F/B) ratio. Generally, these studies have shown a decline in this ratio, indicative of dysbiosis, which could potentially trigger immune activation and neuroinflammation.[180,181] It is noteworthy that the alterations in these microbes appear to differ among ALS subtypes: spinal-onset cases display an increase in fecal F/B ratios, whereas bulbar-onset types reveal a decrease in oral microbiota, implying that local microbial profiles may have varying effects on disease phenotype.[182] Additionally, a lower F/B ratio has been linked to cognitive decline in ALS, reinforcing the connection between gut microbiome imbalance, immune dysfunction, and neurodegeneration.[183,184] Nevertheless, because both phyla contain beneficial and harmful species, a more nuanced taxonomic and metabolic understanding is needed. Such information would be crucial for developing viable hypotheses regarding how immune signals derived from the gut may affect ALS pathology and could introduce new therapeutic pathways based on the microbiota–brain–immune triad.

Furthermore, a reduced presence of butyrate-producing bacteria in ALS has emerged as a distinctive characteristic noted in both clinical and preclinical studies, suggesting that butyrate may play a role in the disruption of gut–immune–brain homeostasis.[185,186] To date, studies on ALS have shown a low abundance of significant pro-butyrate taxa such as *Roseburia intestinalis*, *Eubacterium rectale*, *Anaerostipes*, and *Faecalibacterium*, which are recognized for their immunomodulatory and neuroactive functions.[183] Additionally, a similar distribution of certain butyrate-producing taxa has been observed in ALS animal models, indicating that this specific microbial signature may be conserved to some extent.[187,188] Conversely, the presence of Dorea, a genus associated with pro-inflammatory responses, shows a positive correlation with ALS in both human studies and animal models.[189,190]

Moreover, as previously highlighted, butyrate can traverse the compromised BBB in NDs like ALS and can impact microglial activation by encouraging resident CNS immune cells to transition from a pathogenic M1 pro-inflammatory state to a neuroprotective M2-like state.[191,192] In ALS, both microglia and astrocytes become excessively activated, releasing cytokines such as IL-1β, TNF-α, and IL-6, which further exacerbate the degeneration of motor neurons. Consequently, the reduction of butyrate-producing microbes may lead to increased microglial activation, reinforcing neuroinflammatory cycles.[193,194] Notably, the genus *Dorea*, which is elevated in ALS cases, has been linked to both intestinal and systemic

inflammation and may foster a pro-inflammatory environment by shifting immune balance, as *Dorea* has been shown to encourage the production of IL-17- and interferon-γ-producing T cells.[195,196] These mechanisms imply that dysbiosis related to ALS may sensitize both the innate and adaptive immune responses, potentially affecting both gut and brain health. When we consider all these insights together, they underscore a significant relationship between imbalances in gut microbiota, the decline in regulatory immune cell functionality, and heightened pro-inflammatory signaling in ALS. By further exploring the interactions among these elements, particularly focusing on microbial metabolism, immune cell flexibility, and neurodegeneration, we may uncover new avenues for developing therapies aimed at restoring equilibrium between the gut, immune system, and brain.

Multiple sclerosis (MS)

MS is not only a chronic autoimmune condition affecting the brain and spinal cord primarily in young adults, but it is also increasingly linked to dysregulations in the GBA.[197,198] These dysregulations, frequently observed in autoimmune diseases, are thought to lead to immune dysregulation and heightened oxidative stress. In MS, dysbiosis of gut microbiota and changes in metabolite production may hasten the progression of the disease by activating inflammasomes, maintaining neuroinflammation, and contributing to ongoing demyelination.[199,200] The cumulative impact of demyelination combined with oxidative stress is believed to increase the vulnerability of the CNS, resulting in irreversible neurological impairments through immune-mediated processes.[201,202]

Recent functional studies have aimed to identify specific gut bacteria involved in the development of MS. In this research, investigators minimized genetic and environmental factors by studying monozygotic twins with differing health outcomes related to MS. The gut microbiota analysis revealed more than fifty unique bacterial taxa with varying levels of abundance. Researchers transferred ileum microbiota from specific twins into GF T cell receptor-transgenic mice genetically predisposed to develop MS-like disease upon microbial colonization. The disease manifested at significantly higher rates in mice that received microbiota from MS patients compared to those given gut material from their healthy twin siblings. The findings indicated that two species from the *Lachnospiraceae* family, *Eisenbergiella tayi* and *Lachnoclostridium*, were key contributors to the increased risk of disease.[203] This immune process is heavily influenced by gut dysbiosis in MS and involves the shifting of T cell subsets.[204]

A consistent imbalance between pro-inflammatory Th17 cells and Tregs has been observed in both MS patients and experimental models.[205,206] Dysbiotic microbial populations tend to enhance Th17 cell proliferation, which secrete IL-17 and contribute to CNS inflammation, while simultaneously diminishing the quantity or efficacy of Tregs.[207,208] This discrepancy between Th17 cells and Tregs fosters an environment conducive to autoimmune responses, vital for both the initiation and progression of MS.[209,210] Another probable mechanism is molecular mimicry, where microbial antigens resemble self-antigens present in the CNS. Certain gut microorganisms can generate peptides that imitate components of myelin, resulting in the activation of autoreactive T cells that can react with host tissues.[211,212] This disruption of immune tolerance can instigate autoimmunity, further connecting gut microbiome composition to the pathology of MS.[213,214]

Notably, gut microbiota can be viewed as dynamic environmental factors that affect disease activity in MS. Long-term studies, some lasting as long as 90 days, have observed changes in microbial profiles prior to clinical relapses. This indicates that, while variations in microbiota may act as predictors of disease flare-ups, they also play an active role in the intensification of inflammatory bowel disease.[215,216] Microbial metabolites, especially SCFAs like butyrate and propionate, are increasingly recognized as vital regulators of both gut and systemic immune equilibrium. A decrease in these metabolites can impair the development of Tregs, affect the integrity of the BBB, and initiate pro-inflammatory signaling, all of which contribute to the aggravation of neuroinflammatory processes.[217,218]

To summarize, the gut–immune–brain triad is vital in shaping the pathology of MS through a range of interrelated mechanisms, such as microbial-induced T cell polarization and molecular mimicry, along with the active regulation of disease activity through microbial signals. Examining these interactions between microbes and the immune system reveals promising possibilities for innovative treatments of MS that aim to restore gut microbial balance and uphold immune homeostasis. Figure 2 illustrates how distinct microbial, immune, and neural alterations in AD, PD, ALS, and MS converge on shared pathways—including gut dysbiosis, microglial activation, barrier dysfunction, and immune imbalance—thereby underscoring the gut–brain–immune triad as an integrative framework in neurodegeneration.

Neuroinflammation: A converging mechanism of the gut–brain–immune axis

Neuroinflammation is increasingly acknowledged as a crucial point of interaction in the complex relationship between gut microbiota, the immune system, and the CNS. Once thought to be an organ protected from immune activity, the brain is now recognized for its diverse immune environment, which includes resident microglia and adaptive immune cells such as $CD4^+$ and $CD8^+$ T lymphocytes. These immune cells communicate with neurons both directly through the release of cytokines and membrane-bound receptors and indirectly by influencing glial activity, particularly that of microglia and astrocytes.[219,220] This interaction plays a vital role not only in maintaining neurophysiological balance but also in the progression of diseases. New findings indicate that these central immune cell populations respond to signals originating from the gut, such as microbial metabolites and inflammatory mediators, positioning the gut–brain–immune triad as central to the regulation of neuroinflammation.[221,222]

Metabolites derived from gut microbiota comprise a diverse array of molecules, including SCFAs, neurotransmitter analogs, structural elements like LPS, and molecular mimics, which can traverse the intestinal barrier and enter systemic circulation, thereby influencing immune responses both in the periphery and within the CNS.[223,224] Among these metabolites, SCFAs play a crucial role as immunomodulators. They affect microglial activation, shape immune responses in the periphery, and balance inflammatory T helper cells (Th1, Th17) with Tregs, along with their associated cytokine profiles.[225] The impact of SCFAs is highly context-dependent. For instance, while butyrate can promote anti-inflammatory responses and support glial homeostasis, it might also lead to increased cytokine production or immune cell infiltration in the CNS under specific pathological conditions.[226,227] In addition to SCFAs, microbial byproducts like LPS can activate pattern recognition receptors such as toll-like receptor 4 on peripheral immune cells and CNS microglia, initiating pro-inflammatory signaling pathways. This immune activation has the potential to enhance neuroinflammatory responses even without direct microbial inva-

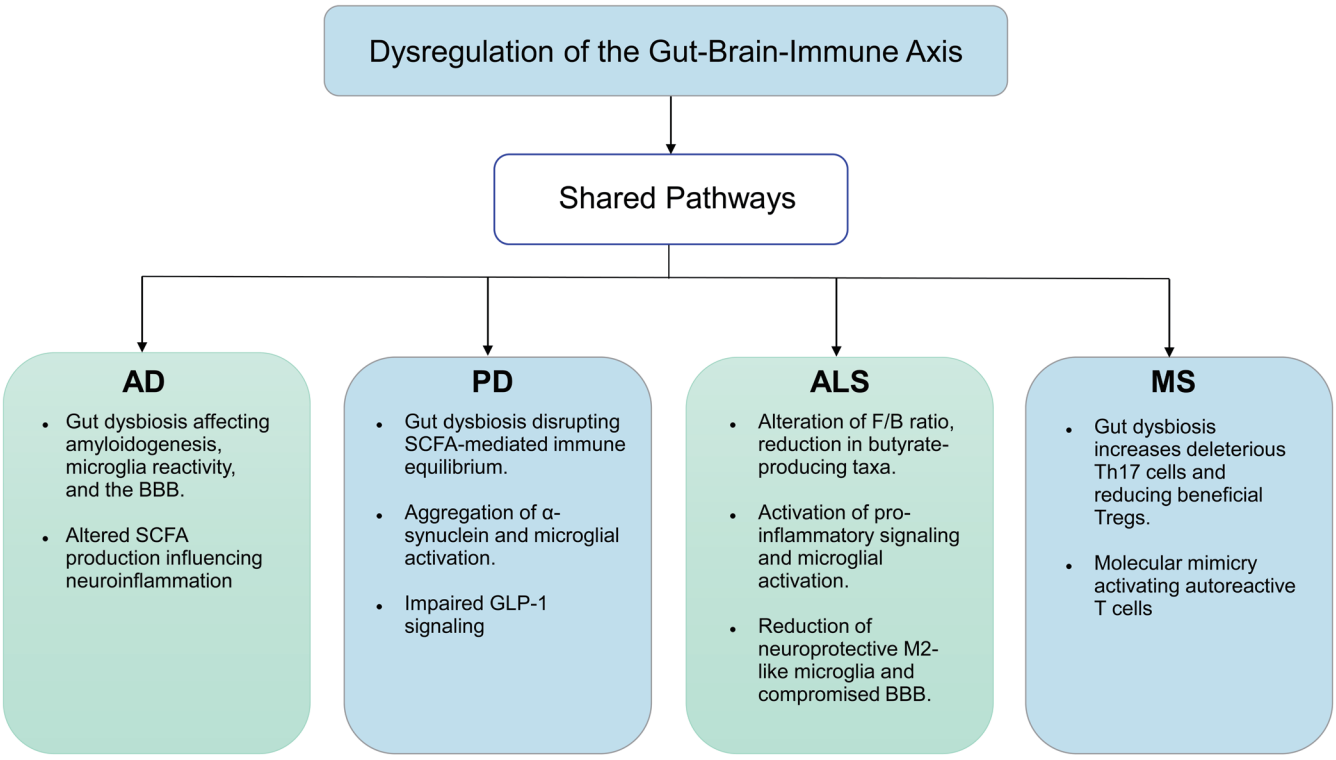

Fig. 2. Disease-specific mechanisms of the gut–brain–immune triad in neurodegenerative diseases (NDs). This illustration depicts the shared pathological pathways of gut dysbiosis, immune system impairment, and central nervous system (CNS) dysfunction involved in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). Dysbiosis of gut microbiota in AD affects amyloidogenesis, microglial activation, and the integrity of the blood–brain barrier (BBB), along with variations in short-chain fatty acid (SCFA) synthesis that may ultimately lead to neuroinflammation. PD is marked by gut dysbiosis, aggregates of α-synuclein, activated microglia, and disrupted glucagon-like peptide (GLP)-1 signaling. In ALS, the ratio of Firmicutes to Bacteroidetes (F/B) changes, with the loss of specific butyrate-producing taxa linked to proinflammation and microglial activation, along with reduced neuroprotective M2-like microglia, suggesting a decline in BBB functionality. In MS, pathophysiologically characterized dysbiosis allows the proliferation of pro-inflammatory T helper 17 (Th17) cells, diminishes regulatory T cells (Tregs), and involves molecular mimicry that may activate autoreactive T cells. Collectively, these characteristics reflect a convergence of microbial, immune, and neural disturbances that can be leveraged for the propagation of ND phenotypes.

sion.[228] Conversely, certain microbial components, such as polysaccharide A from *Bacteroides fragilis*, reduce neuroinflammation in murine MS models[229]; human translation remains limited by delivery challenges and strain-specific effects. Polysaccharide A and related polysaccharides are currently being explored as potential therapeutic agents for NDs like MS, where excessive inflammation is a key factor.[230] Molecular mimicry establishes another connection between gut microbial signals and CNS immunity, as microbial antigens can activate autoreactive T cells that migrate into the CNS and induce inflammation through both antigen-specific and bystander mechanisms.[231]

Beyond affecting immune cell function, the gut microbiota also plays a role in the movement of immune cells. Specific T cell subsets, including Th17 and γδ T cells, are activated in the gut and later migrate to the meninges or CNS in response to injury or infection.[232,233] Research indicates that modifying the gut microbiota through antibiotics or fecal microbiota transplantation impacts the quantity and characteristics of these immune cells, which in turn affects vulnerability to neuroinflammation.[234,235] Therefore, the gut acts both as a foundation for immune development and a source of pro-inflammatory cells that can be activated during neurological diseases.[55]

In addition to humoral and cellular processes, the vagus nerve serves as a direct neural pathway connecting the gut and the brain. Microbial byproducts and inflammatory markers can modify vagal tone, thereby impacting brainstem functions and neuroimmune communication.[236,237] Research using animal models has demonstrated that stimulating the vagus nerve can reduce neuroinflammatory reactions, while vagotomy can worsen them.[238,239] Certain beneficial bacteria also produce neuroactive substances such as gamma-aminobutyric acid, which may influence CNS function through vagus-mediated or systemic pathways.[179,240] These findings underscore the critical function of neural signaling in conveying gut-derived signals to induce immune reactions in the brain.

Importantly, epigenetic processes serve as a crucial link between microbial signals and enduring alterations in immune and neural functions.[241,242] As previously mentioned, SCFAs such as butyrate function as histone deacetylase inhibitors, thereby altering chromatin configuration and transcriptional profiles in immune and glial cells.[57–60,243,244] Metabolites produced by one-carbon metabolism influence DNA methylation and histone modifications, affecting the differentiation of immune cells and their inflammatory capacities when they enter the CNS.[245] Early exposure to microbes during pivotal stages of brain development can establish epigenetic marks that determine future susceptibility or resilience to neuroinflammation.[246] These epigenetic modifications are not static; ongoing inflammatory triggers, frequently originating from gut dysbiosis, can lead to enduring changes in microglia

and monocytes, fostering a condition of "trained immunity" that sustains inflammation in the CNS.[247,248] In addition, non-coding RNAs, particularly miRNAs modulated by the gut microbiota, play critical roles in regulating host gene expression, influencing essential cellular processes such as cytokine signaling, synaptic plasticity, and responses to cellular stress.[249,250] Several microbiota-responsive miRNAs are implicated in the bidirectional signaling of the gut–immune–brain triad. Gut microbial communities influence host miRNA expression through bioactive metabolites, including SCFAs and indole derivatives. These metabolites modulate miRNA expression in intestinal epithelial and immune cells, shaping mucosal immune responses and contributing to systemic inflammatory tone.[251,252]

These miRNAs can be released into circulation via extracellular vesicles, such as exosomes, and in some cases, may cross the BBB to influence gene expression within microglia, astrocytes, and neurons.[253,254] Specific miRNAs altered under dysbiotic conditions, such as miR-155, miR-146a, and miR-21, have been implicated in neuroinflammatory cascades by modulating NF-κB signaling and downstream cytokine production, linking peripheral immune activation to central neuroimmune dysregulation.[255–257] Additionally, miRNA-mediated regulation of neurotrophic factors, such as brain-derived neurotrophic factor, may directly influence synaptic function and plasticity, contributing to cognitive impairment observed in NDs.[258,259] This miRNA-based cross-talk underscores the intricate interdependence between gut microbial ecology and brain homeostasis and highlights a promising platform for developing diagnostic biomarkers and targeted therapeutic strategies to modulate the gut–immune–brain triad in NDs. Thus, epigenetic regulation provides a compelling framework for understanding how reversible environmental factors, such as diet, infections, or stress, conveyed through the microbiome, can lead to lasting neuroinflammatory consequences.[260,261]

In summary, neuroinflammation should not be regarded solely as a subsequent effect of disease but as a dynamic, integrative process regulated by the gut–brain–immune triad. The immune system, microbiome, and CNS are interconnected elements of a precisely balanced network; any disruption, through microbial dysbiosis, immune dysfunction, or neuronal impairment, can initiate or exacerbate brain inflammation. A detailed understanding of how microbial metabolites, immune cell movement, vagal signaling, and epigenetic changes function context-dependently provides a strong foundation for identifying new therapeutic targets aimed at reestablishing balance within this intricate triad.

Limitations of the study

As evidence increasingly supports the critical role of the gut–brain–immune triad in NDs, its translation into clinical practice remains hindered by several key limitations. Foremost among these is the persistent challenge of disentangling causation from correlation. While associations between gut dysbiosis, immune dysfunction, and CNS pathology are becoming more apparent, most existing studies, particularly those in human subjects, lack the mechanistic depth required to determine directionality or establish definitive causal relationships. A substantial proportion of the current evidence is derived from preclinical models, including GF or antibiotic-treated rodents. While these models offer important insights, they fail to capture the complexity and chronic progression of human NDs, which are shaped by multifactorial influences—genetic, environmental, and behavioral—that accumulate over time. Furthermore, rodent models rarely replicate the slow, progressive pathology characteristic of disorders such as AD or ALS, limiting their translational relevance.[262,263]

Consequently, there is an urgent need for more physiologically relevant and dynamic experimental systems, such as brain–gut organoids or organ-on-a-chip platforms (microphysiological systems), to better elucidate the evolving and informative interactions within the gut–brain–immune interface in human neurodegeneration.[264,265] A further complication arises from the substantial interindividual variability in gut microbiota composition, driven by factors including host genetics, age, dietary patterns, geography, medication use, comorbidities, and lifestyle differences. These variables not only affect microbial ecology but also hinder reproducibility and reduce the external validity of findings across cohorts. This complexity makes it challenging to identify consistent, disease-specific microbial signatures or therapeutic targets.[266,267]

Moreover, microbiome research is limited by technical and methodological inconsistencies, such as the lack of standardized protocols for sample collection, sequencing techniques, data normalization, and microbial taxonomy annotation. These discrepancies introduce biases, restrict cross-study comparability, and impede robust meta-analyses.[268,269] Such limitations are further compounded by the underrepresentation of certain NDs, particularly ALS and early-stage AD, in microbiome research, leading to knowledge gaps and an incomplete understanding of disease-specific gut–brain–immune dynamics.

Adding to this complexity is the emerging recognition of gut-derived hormones beyond GLP-1, challenging the prevailing notion that the gut endocrine system primarily influences ND pathophysiology through GLP-1 signaling.[166] Although GLP-1RAs, such as semaglutide, have shown considerable therapeutic promise, their predominantly peripheral distribution and limited ability to cross the BBB suggest that their observed neuroprotective effects may be mediated via peripheral gut–brain pathways, such as modulation of immune responses or behavioral regulation, rather than through direct actions within the CNS.[166,270,271] These observations raise important questions regarding the mechanisms and extent to which gut-derived hormonal signals contribute to the onset and progression of NDs.

Another major challenge is the current over-reliance on cross-sectional study designs in the literature. Cross-sectional data fail to capture the dynamic, longitudinal changes in gut microbial communities and immune responses that occur during the onset and progression of NDs.[272] Given that clinical symptoms of NDs typically manifest only after a prolonged preclinical phase—spanning years to decades—cross-sectional analyses are inherently limited in their ability to distinguish causation from consequence. During this extended preclinical window, the gut microbiota are continuously shaped by multiple factors, including aging, diet, environmental exposures, medication use, and overall health status. As a result, in the absence of prospective, longitudinal studies that track microbial and immunological changes from the prodromal through symptomatic stages, it remains unclear whether observed dysbiosis represents a causal trigger, an adaptive response, or an unrelated epiphenomenon.[273,274]

Another previously underexplored dimension is the role of epigenetic regulation in modulating gut–brain–immune interactions. Emerging evidence indicates that microbiota-derived metabolites, including SCFAs and tryptophan catabolites, can influence epigenetic mechanisms such as DNA methylation, histone acetylation, and the regulation of non-coding RNAs.[275,276] However, the downstream consequences of these epigenetic modifications on neural and immune function remain largely unknown. Moreover, it is still

unclear whether these changes are confined to intestinal epithelial cells or also occur in peripheral immune cells and glial populations within the CNS. Understanding the spatiotemporal characteristics of these epigenetic alterations is essential for elucidating their functional relevance in NDs.[277]

Lastly, the bidirectional nature of the gut–brain–immune triad introduces a feedback mechanism that is often overlooked. NDs can induce perturbations in gut microbial composition and compromise intestinal barrier integrity through mechanisms such as psychosocial stress-induced dysregulation of the autonomic nervous system, impaired vagal signaling, and pharmacologically induced dysbiosis. These disruptions can, in turn, reinforce neuroinflammatory loops that exacerbate disease progression.[278,279] Failure to account for these recurrent, bidirectional interactions may reduce the effectiveness of therapeutic interventions and obscure critical windows of opportunity for treatment.

Taken together, although the relationship between the gut, brain, and immune system provides an intriguing basis for comprehending NDs, its effective application is constrained by diverse research methods, a lack of clear causal relationships, and inadequate incorporation of epigenetic and hormonal knowledge.

Significance of the review

Recent reviews published in 2025 underscore renewed therapeutic promise associated with targeting the microbiota–gut–brain triad in NDs through next-generation probiotics, microbiota-derived postbiotics, and engineered microbial consortia. Although preclinical studies, particularly in AD and PD models, have demonstrated efficacy in reducing neuroinflammation, enhancing cognitive function, and restoring BBB integrity, the field continues to face a significant translational gap. Notably, large-scale, longitudinal human trials remain scarce; interindividual variability in microbiome composition challenges the feasibility of universal therapeutic approaches; and reproducible microbial biomarkers indicative of ND progression have yet to be clearly established. Moreover, recent literature has begun to consider hormonal and epigenetic components as potential therapeutic avenues. However, these aspects are often addressed superficially, with limited mechanistic depth.

Against this backdrop, the present review poses significant inquiries by examining overlooked elements of the gut–brain–immune triad, emphasizing the spatiotemporal dynamics of microbiota-driven epigenetic regulation and the newly identified function of non-GLP-1 gut hormones in modulating immune and neural pathways. It highlights the often-overlooked bidirectional feedback loops between gut dysbiosis and neurodegeneration, which have received little attention in the current literature. By dismantling isolated disciplinary viewpoints and highlighting the mechanistic connections that have been neglected, this review fosters a comprehensive framework that facilitates causally informed and individualized treatment strategies for NDs. In this context, Table 1 compiles essential information on each ND, including targeted pathways, therapeutic strategies, and the extent of supporting evidence, drawing attention to areas requiring further translational research.

Future directions

Microbial metabolites have the potential to influence epigenetic changes in host cells, offering a mechanism for long-lasting neuroimmune modulation—effects that might even be transmitted across generations in some instances. This area of study could pave the way for personalized microbiome-based treatments designed according to specific microbial and immune characteristics. Nevertheless, these approaches will require thorough validation through well-structured clinical trials before broad implementation. Future research should also prioritize the systematic investigation of vagal and humoral signaling pathways. To enhance reproducibility and enable meaningful cross-study comparisons, the implementation of standardized methodologies is essential, such as the Earth Microbiome Project protocols for microbiome sequencing and the Minimum Information about any (x) Sequence (MIxS) standards for metadata reporting.[280,281] Furthermore, the development and adherence to robust ethical guidelines will be critical to ensure the safe, responsible, and effective translation of microbiome-based interventions into clinical practice.

Additionally, longitudinal studies in humans that combine microbiome analysis with multi-omics techniques are crucial for understanding how microbial communities vary and shift across different states, especially concerning the onset and development of neurodegenerative and neuroimmunological conditions. There should be a stronger focus on monitoring temporal changes in gut microbiota during the prolonged prodromal phase, as early dysbiosis may significantly influence the course of the disease. Moreover, new experimental models like brain–gut organoids and microfluidic systems are becoming important tools for exploring causal mechanisms in contexts that closely mimic physiological conditions. Importantly, the impact of gut-derived signals on neural stem cells deserves further exploration, considering their potential contributions to neuroregeneration and tissue repair in NDs.

Conclusions

The gut–brain–immune interface represents a critical, yet historically underrecognized, component in the pathophysiology of NDs, including AD and PD. A growing body of evidence implicates perturbations in gut microbial composition and function in promoting systemic and CNS inflammation, compromising the integrity of the BBB, and disrupting neuroimmune communication. Microbial metabolites, particularly SCFAs, are increasingly recognized as modulators of host immune responses and neuroprotective signaling pathways. Notably, reduced SCFA production in individuals with NDs has been correlated with elevated pro-inflammatory cytokine levels and accelerated disease progression. Moreover, gut microbiota-derived components, such as bacterial amyloids and misfolded α-synuclein, along with alterations in gut-derived hormonal signaling (e.g., GLP-1 pathways), further support the hypothesis that GI dysfunction may contribute to the initiation and progression of NDs. Despite the growing body of evidence linking gut microbiota alterations to ND pathology, direct causality between microbiome changes and disease progression has not yet been conclusively established. Much of the current understanding is derived from preclinical models, and substantial inter-individual variability in microbiome composition presents a significant challenge to translational research and causal inference in humans. Although interventions such as probiotics, postbiotics, and dietary modifications show therapeutic potential, existing clinical trial data remain limited in scale, statistical power, and reproducibility. Accordingly, there is an urgent need for longitudinal, well-controlled human studies, ideally complemented by mechanistically informative *in vitro* models, such as gut–brain organoids, to rigorously investigate causal pathways and therapeutic efficacy. Looking ahead, a precision medicine approach that integrates microbiome-targeted interventions with immunological and epigenetic

Table 1. Therapeutic strategies targeting the gut–brain–immune axis in neurodegenerative diseases: Key studies

Disease	Target pathway	Potential intervention	Current evidence	Translational gaps
Alzheimer's disease (AD)	Production of SCFA (butyrate); neuroinflammation; integrity of the BBB	Sodium butyrate intake; fiber in diet; time-restricted eating (TRE); probiotic B. pseudolongum	Studies using animal models, such as 5xFAD mice (which are genetically modified to contain five mutations linked to familial AD), show that NaB reduces amyloid-β levels by around 40% and improves cognitive abilities; TRF (a dietary method that limits food consumption to a designated timeframe) promotes the proliferation of B. pseudolongum and raises SCFA (particularly propionate) concentrations; observational studies suggest a correlation between dietary butyrate and cognitive health in older populations	There are no controlled human studies involving butyrate or B. pseudolongum in AD, and the ideal dosage, administration method, and long-term safety are still unclear. For example, research on humans identified a positive link between increased dietary butyrate consumption and improved cognitive performance in older individuals, encompassing assessments of executive function and memory, according to a recent study released in 2025 by the National Institutes of Health (NIH). Nonetheless, this was an observational study rather than a controlled intervention
Parkinson's disease (PD)	Intestinal dysbiosis; inflammation; α-synuclein clustering; reduction of SCFAs	Probiotics (e.g., L. plantarum PS128, L. paracasei Shirota); dietary adjustments; designed biotherapeutics; FMT	Meta-analyses of RCTs (n ≈ 750–840) indicate enhancements in motor scores, gastrointestinal symptoms, mood, and inflammatory indicators; strain-specific RCTs reveal cytokine modulation and relief from symptoms; engineered probiotic trials are scheduled for 2024 in Australia. Recent research also indicates that certain probiotic strains might lower pro-inflammatory cytokine levels and improve both motor and non-motor symptoms in individuals with PD, addressing frequent concerns like fatigue and constipation	More extensive and prolonged RCTs are necessary to validate disease-modifying impacts; efficacy related to specific strains remains uncertain; FMT's safety and effectiveness for PD have not been determined
Multiple sclerosis (MS)	Th17/Treg equilibrium; intestinal permeability; SCFA-driven immune modulation	Dietary fiber; SCFA (such as propionate) supplementation; TUDCA; FMT	SCFA supplementation diminished disease severity and boosted Tregs in EAE models; clinical trials indicate that propionate raises Tregs and lowers relapse rates and brain atrophy in pwMS; an early-phase trial in progressive MS indicated that TUDCA was safe, adjusted immune markers, but did not demonstrate notable clinical progress over 16 weeks	Requires larger RCTs with clinical outcomes; the long-term adherence to dietary/SFCA protocols is unclear; FMT donor selection and safety must be standardized
ALS	Neuroinflammation; intestinal permeability; metabolic signaling	A. muciniphila enhancement; SCFA treatment; modified probiotics	In SOD1-G93A ALS mice, A. muciniphila, butyrate, and SCFA-boosting probiotics enhanced gut barrier integrity, lowered neuroinflammation, and extended survival by promoting autophagy and mitochondrial function	No human studies focus on microbiota in ALS; the mechanistic connection to clinical advantages remains unclear; the pathway for translation is not yet established
Huntington's disease	Gut dysbiosis; systemic inflammation	Diet rich in fiber; polyphenolic compounds (e.g., curcumin); FMT (theoretical aspect)	While there aren't many dedicated neurodegeneration *in vivo* models based on polyphenols, murine studies in similar frameworks have demonstrated the ability of polyphenols (e.g., grape polyphenols, quercetin, and EGCG) to change gut microbiota (e.g., increase Akkermansia and SCFA-producers), enhance barrier integrity, and decrease pro-inflammatory cytokines like TNF-α and IL-6	Lack of clinical trials involving humans; ambiguous mechanisms; no established translational pathway
Autism spectrum disorder (ASD)	Production of neurotransmitters by microbes; dysregulation of the immune system	Bacteroides fragilis as a probiotic; nutritional changes; FMT	Rodent models demonstrate behavioral enhancements with B. fragilis; phase 1 trial with AB-2004 (a microbial metabolite adsorbent) decreased toxic metabolites and anxiety symptoms in teenagers with ASD	More extensive, regulated studies are required; developmental safety and long-term neuroimmune effects need to be evaluated in child populations

EAE, experimental autoimmune encephalomyelitis (murine model of MS); EGCG, epigallocatechin-3-gallate; FMT, fecal microbiota transplantation; IL-6, interleukin-6; NaB, sodium butyrate; pwMS, people with multiple sclerosis; RCT, randomized controlled trial; SCFA, short-chain fatty acids (e.g., butyrate, propionate, acetate); TNF-α, tumor necrosis factor-alpha; TUDCA, tauroursodeoxycholic acid.

modulation may offer more specific and effective strategies for the prevention and management of NDs. However, such approaches must be guided by robust, reproducible evidence and implemented with careful consideration of the inherent complexity and inter-individual heterogeneity of both the microbiome and ND processes.

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Conflict of interest

The authors have nothing to declare.

Author contributions

Conceptualization (SKC), formal analysis (SKC), original draft preparation (SKC), writing–review and editing (SKC, DC), project supervision (SKC), project administration (SKC), and funding acquisition (SKC). Both authors have approved the final version and publication of the manuscript.

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