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Original Research Article

Understanding the Human Gut Microbiota impacts in Neurodegenerative Disorders: A Correlative Approach

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Abstract:

A person's physiology is mostly influenced by the microbiota present in their gut. Studies revealed myriad patterns of microbiome composition at various stages of life, with major alterations in the dominating phyla and species identified as age progresses. Notably, the quantity of Actinobacteria declines after weaning, whereas Firmicutes and Bacteroidetes increase in prevalence, particularly in older individuals. When the gut microbiota is compromised, the entire body is impacted. Diverse human illnesses are related to the onset and progression of gut microbiota dysbiosis. During the last ten years, research has been aimed at the interactions that occur between the gut microbiota and other body systems, such as the immunological, neurological, and metabolic systems. Neurodegenerative diseases (NDs) are defined as the gradual decline in selectively susceptible neurons. Worldwide, people face significant medical and public health challenges as a result of degenerative illnesses of the neurological system. Among the most common neurological disorders are Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). These illnesses have a sharp increase in incidence and frequency as people age. There has been increasing curiosity regarding the connection between brain development and gut bacteria. Germ-free (GF) mice were shown to exhibit higher levels of motor activity and a decrease in anxiety-like responses in comparison to specific-pathogen-free (SPF) mice. The blood–brain barrier (BBB) is crucial in regulating the flow of nutrients, as well as chemicals, between the blood and the brain. The GF mice exhibited higher blood–brain barrier permeability in comparison to SPF mice. The Pavlov pouch, an externalized section of the dog intestine used to research canine digestive processes, was contributed by Ivan Pavlov, who, as well as defining classical conditioning, was also a forerunner in the arena of the gut–brain axis (GBA). He refined the methods by preserving innervation to the intestine section, enabling more precise monitoring of digestive processes in real time over prolonged periods. The GBA, is a two-way interaction that mediates the significant influence of bacteria on physiological processes in the brain. Neurotransmitters and other metabolites are used by the gut–brain axis to engage in bidirectional communication between the brain and the gut. Many clinical and experimental studies have revealed the significance of the microbiota in NDs via different microbial chemicals that travel through the GBA or neurological system from the gut to the brain. The central, autonomous, and enteric neural systems, together with the immunological, endocrine, and metabolic systems, are all involved in the communication process. However, the precise mechanism regulating the signal propagation and stimulating alterations in host diseases is still unknown. Through these pathways, the metabolites of the gut microbiota, which include SCFAs, histamine, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, etc., affect several cerebral physiological functions. An imbalance in the composition of the gut microbiome, causes the brain to receive signals that lead to low-grade inflammation, increased oxidative stress, disturbed energy metabolism, and increased cellular aging. These pathological processes are involved in a variety of neurological diseases.

Keywords: Neurodegenerative, Disease, Micrbiota, Metabolism.

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Introduction

Neurodegenerative disorders encompass a wide range of conditions that result from progressive damage to cells and nervous system connections that are essential for mobility, coordination, strength, sensation, and cognition. NDs affect millions of people worldwide. Although there isn't a complete cure for most of these complex neurological diseases, UT Southwestern offers comprehensive, individualized treatment to help patients manage them. UT Southwestern is actively

involved in the latest research and technology to offer therapies and rehabilitation services that improve symptoms, increase mobility, and enhance the quality of life of patients and family members.

Gastroenterologists may only address the sick digestive organ, whereas the nutritionist may recommend revisions to the kinds and amounts of the food we eat, but often neither of them consider the food-body-emotion interaction. Increasing evidence suggests that the gut microbiota affects different physiological, pathological and behavioral outcomes through modulation of neuroendocrine pathways. Systems biology approaches will also be important in integrating such data with genomic and metabolomic datasets from clinical cohorts with neurological disease to help guide individual treatment selection.

The production of hormones and neuroactive metabolites from the gastrointestinal tract influences distal sites and ultimately results in central activation and behavioural changes. Research into the role of the gut microbiota in modulating brain function has rapidly increased over the past 15 years, albeit chiefly in animal models.

The clinical studies are bolstering the concept of altered microbial composition contributing to the pathophysiology of such diseases. However, the field is nascent, and interpretation of such data is often difficult given that the composition of the microbiota is influenced by various factors such as diet and exercise. Increasing clinical and preclinical evidence implicates the microbiota as a possible key susceptibility factor for neurological disorders, including Alzheimer's disease, autism spectrum disorder, multiple sclerosis, Parkinson's disease, and stroke. The makeup of the gut microbiome and its impact on brain function through the gut–brain axis is highlighted. Dysbiosis, characterized by changes in the gut microbiota's composition, has been linked to the development of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. A Bidirectional communication between the stomach and the brain takes place via a variety of channels, including neurotransmitters and metabolites generated by gut bacteria. We investigate the processes through which dysbiosis causes neuroinflammation, oxidative stress, and neuronal damage, which drive disease development. Potential therapeutic approaches that focus on the gut microbiota, such as antibiotics, probiotics, prebiotics, and fecal microbiota transplantation, are reviewed, with promising preclinical and clinical findings. The balance between the human body and the environment, i.e., what we eat, what we feel and our behavior (emotions) according to the person's personality (genetics) or character. This balance leads to well-being, health, and happiness, while an imbalance leads to illness.

Modern or scientific medicine, as defined by the concepts derived from Descartes' scientific method, has achieved significant advances in the understanding of how our body functions, first at the macroscopic and microscopic level, then followed by biochemical-physiological aspects, and most recently at the molecular level. In the last century, modern medicine has focused more on disease than on health, leading to a fragmentation of our scientific knowledge.

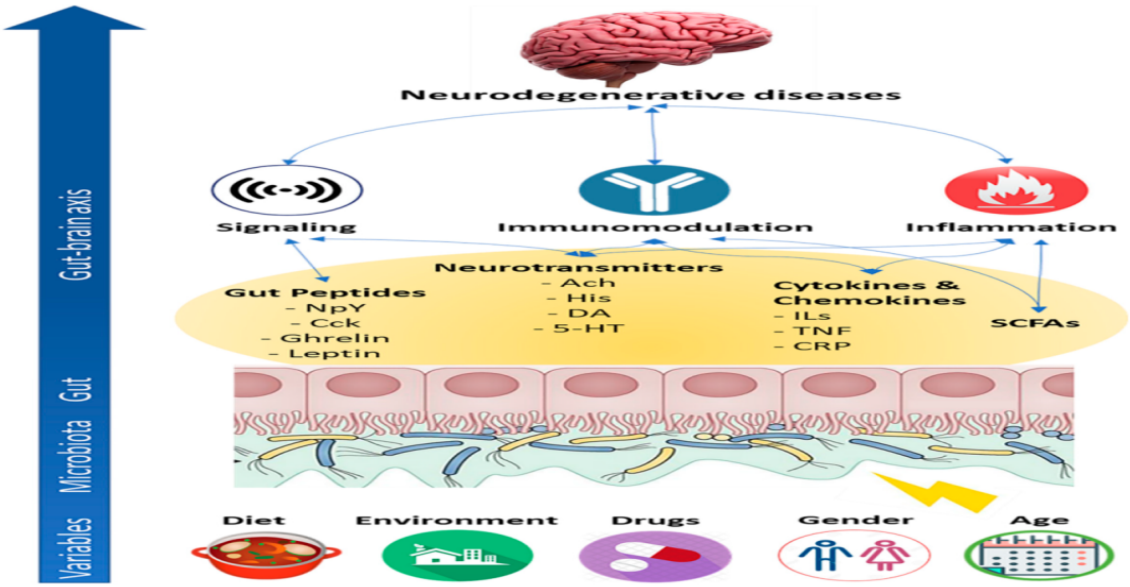

Figure 1: Major mechanisms employed by gut microbiota to impact neurodegenerative diseases

The figure depicts the most relevant endogenous (i.e., age, gender) and environmental (i.e., diet, environment, and drugs) variables affecting gut microbiota composition and functions. In turn, microbiota dysbiosis impacts neurodegenerative diseases through direct production of neuroactive molecules (e.g., short-chain fatty acid (SCFAs), neurotransmitters) and/or stimulation of neuroactive mediator production by the secretory epithelial cell (e.g., Citokynes, chemokine, gut peptides). Examples of neuroactive molecules are mentioned in the figure. Ach: Acetylcholine; His: Histidine; DA: Dopamine; 5-HT: Serotonin; NpY: Neuropeptide-Y; CcK: Cholecystokinin; ILs: Interleukins; TNF: Tumor Necrosis Factor; CRP: C-Reactive Protein [1].

The predominance of aerobic microorganisms throughout perinatal and postnatal development changes after birth. During the first few weeks of life, the microbiota diversifies to produce a diverse microbial community that is dominated by anaerobes. Strict anaerobes make up the majority of the gut microbiota. Even though more than 50 bacterial species have been identified so far, just two of them Bacteroidetes and Firmicutes-dominate the human gut microbiota, with smaller numbers of Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria. The fermentation of indigestible substrates such as food fibers and endogenous intestinal mucus is facilitated by the gut bacteria. The growth of specific microorganisms that generate gases and short-chain fatty acids (SCFAs) is aided by this fermentation. Butyrate, propionate, and acetate are the main SCFAs generated. Higher synthesis of SCFAs has been associated with reduced diet-induced obesity and lower insulin resistance, according to randomized controlled studies.

Neurodegenerative diseases (NDs) are defined as the gradual decline in selectively susceptible neurons. Worldwide, people face significant medical and public health challenges as a result of degenerative illnesses of the neurological system. Among the most common neurological disorders are Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). These illnesses have a sharp increase in incidence and frequency as people age. There has been increasing curiosity regarding the connection between brain development and gut bacteria. Germ-free (GF) mice were shown to exhibit higher levels of motor activity and a decrease in anxiety-like responses in comparison to specific-pathogen-free (SPF) mice. The blood–brain barrier (BBB) is crucial in regulating the flow of nutrients, as well as chemicals, between the blood and the brain. The GF mice exhibited higher blood–brain barrier permeability in comparison to SPF mice.

The enteric nervous system (ENS), a significant component of the ANS, is situated within the GI tract and constitutes a complex mesh of 200 to 600 million neurons facilitating the control of gut functions, including motor activity, secretion, absorption, and immune defense, playing a pivotal role in maintaining gut homeostasis and interacting with the microbiota and host systems [2].

The ENS is anatomically composed of two ganglionated plexuses, the myenteric and submucosal plexus, containing nitrergic and cholinergic neurons [3]. Intrinsic neurons of the ENS commonly communicate with the CNS through the PNS, mainly the vagus nerve, and the SNS, such as the prevertebral ganglia. These complicated intrinsic and afferent neural signals create avenues for factors originating from the gut lumen, potentially encompassing the microbiota, to influence not only intestinal functions but also the CNS. The structure and neurochemistry of the ENS resemble that of the CNS, which is why it often is referred to as the "second brain", and thereby, any mechanisms implicated in CNS dysfunction may also result in ENS dysfunction or vice versa [4].

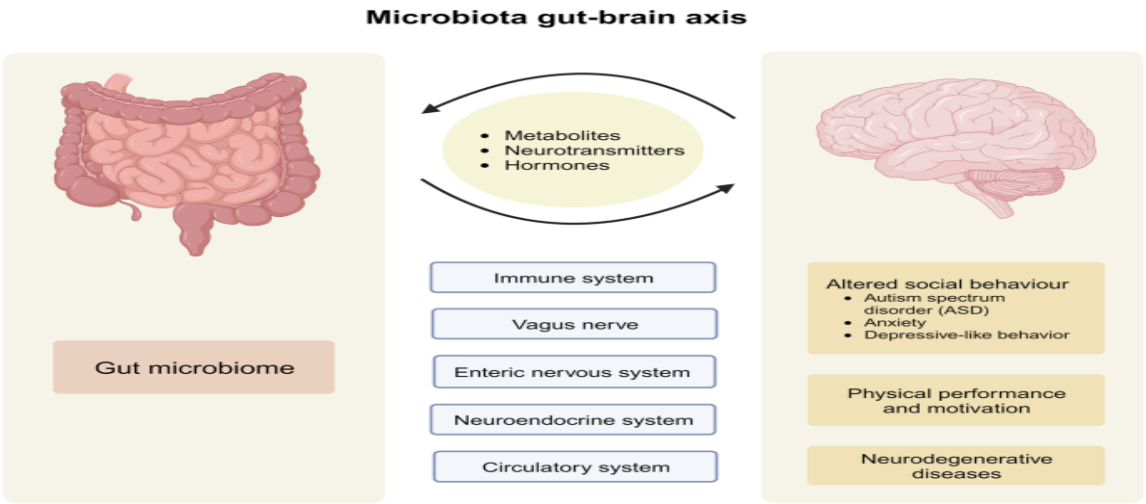

Figure 2: The microbiota–gut–brain axis

The bidirectional communication between the gut microbiome and the brain is mediated by the immune system, vagus nerve, enteric nervous system, neuroendocrine system, and circulatory system. Alterations in gut microbiota have been linked to the development of autism spectrum disorders, anxiety, depressive-like behavior, impaired physical performance, and motivation, as well as neurodegenerative diseases [1].

The gut microbiota significantly influences ENS development and function through the activation of pattern recognition receptors (PRRs) such as toll-like receptors TLR-2 and TLR-4, which recognize microbial lipopolysaccharide (LPS), peptidoglycan, and viral RNA. Studies in TLR-deficient mice have demonstrated changes in ENS functions, including reduced stool output, water content, and gut motility [5]. Germ-free (GF) mice have exhibited a disrupted ENS structure, reduced enteric neurons, compromised gut motility, and impaired sensory signaling. GF mice also exhibit abnormal neurochemistry and insufficient influx of enteric glial cells into the intestinal mucosa [6]. These observations are mirrored in mice with antibiotic-induced gut microbial dysbiosis [7]. The gut microbiota promotes serotonin biosynthesis by enterochromaffin cells, vital for mucosal and platelet function [8]. Additionally, the gut microbiota can also produce neurotransmitters and metabolites like GABA, histamine, catecholamines, acetylcholine, and short-chain fatty acids (SCFAs), further shaping ENS activity. On the contrary, the ENS seems to possess the ability to exert an influence on the gut microbiota. An investigation utilizing a transgenic zebrafish model with impaired ENS function unveiled a notable alteration in the composition of the GI microbiota, shifting it towards a proinflammatory microbial profile. Intriguingly, the introduction of ENS precursors through transplantation reversed the microbiota back to its normal state [9].

These findings suggest a bidirectional interaction between the gut microbiota and the ENS, highlighting the complex interplay between these systems. Moreover, ENS has now been implicated in NDDs [10], including AD and PD, typically considered primary CNS conditions. This underscores once again the vital role of ENS in intricate communication between the gut and the brain.

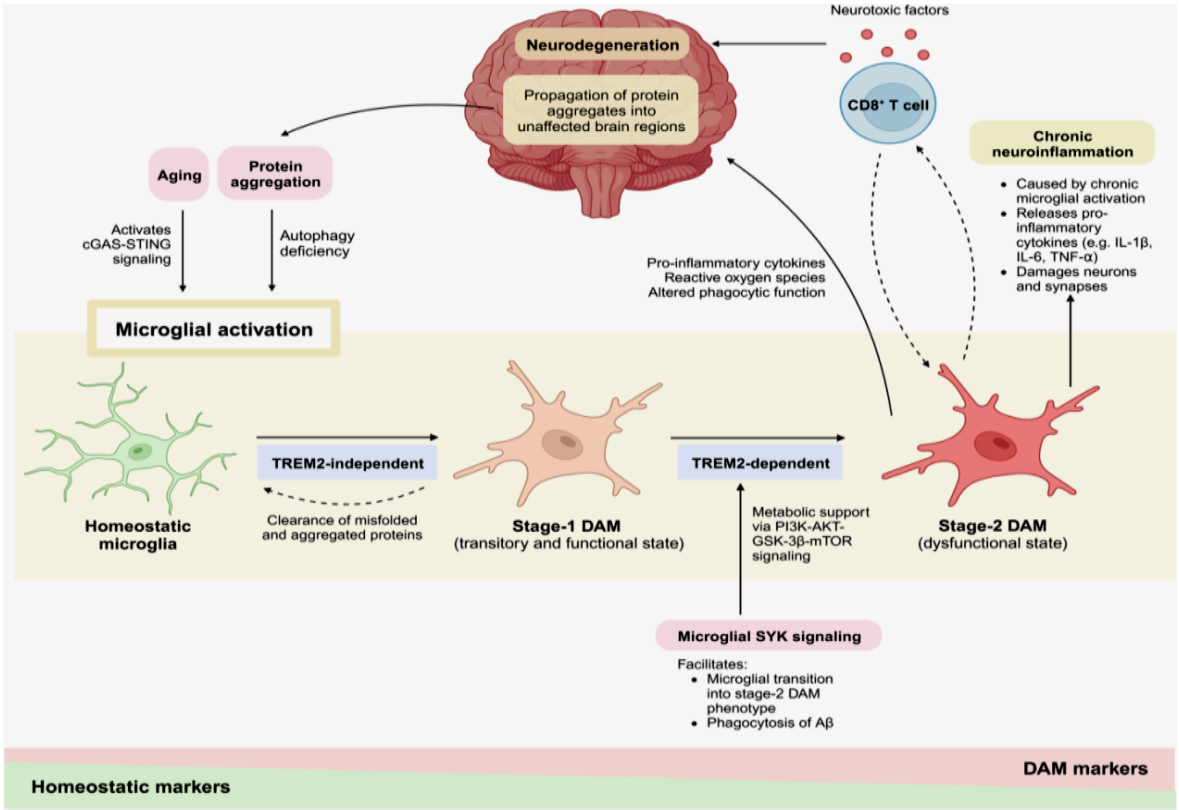

Figure-3: Microglial activation and neurodegeneration

Aging induces microglial activation by activating the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway. Misfolded proteins and protein aggregates induce microglial activation by impairing microglial autophagy. Stage-1 DAM represents a transitory and functional subtype with a higher capacity of phagocytosis initiated by a TREM2-independent mechanism, whereas stage-2 DAM represents a dysfunctional state initiated by a TREM2-

dependent mechanism. The microglial spleen tyrosine kinase (SYK) signaling provides metabolic support to facilitate microglial transition into stage-2 DAM. Maladaptive microglial-T-cell signaling drives neurodegeneration by releasing neurotoxic factors. Microglial activation creates a feed-forward vicious cycle that aggravates neurodegeneration as activated microglia contribute to the propagation of protein aggregates into unaffected brain regions [1].

Neuroendocrinological Concept of Gut Brain Approach:

The hypothalamic–pituitary–adrenal (HPA) axis is considered an essential neuroendocrine pathway integral to GBA communication, orchestrating physiological adaptation to stress. During stress, the hypothalamus initiates the synthesis and secretion of corticotropin-releasing hormone (CRH), which serves as the primary regulatory factor for the HPA axis. CRH subsequently traverses to the anterior pituitary gland, where it binds to its corticotropin receptor, thereby inducing the release of adrenocorticotropic hormone (ACTH) into the systemic circulation.

ACTH stimulates the adrenal gland to synthesize and secrete glucocorticoids (cortisol in humans and corticosterone in rodents), serving as downstream effectors of the HPA axis. These glucocorticoids regulate physiological alterations through ubiquitously disseminated intracellular receptors to meet metabolic, physical, and psychological demands under stress. Nevertheless, both excessive and insufficient activation of the HPA axis leads to psychophysiological disorders [11].

Specifically, appropriate levels of glucocorticoids are essential for proper neurodevelopment, and cognitive processes such as learning and memory [12]. Experimental models investigating stress have demonstrated a correlation between the HPA axis and alterations in microbiota composition as well as its metabolites [13]. Conversely, the microbial modulation of the HPA axis also affects glucocorticoid concentrations. Modulating gut microbiota through the administration of probiotics and prebiotics has been shown to ameliorate the stress-dependent increase in corticosterone levels [14]. Considering the widespread distribution of glucocorticoid receptors across multiple organs, including the GI tract and the CNS, as well as on various cells such as neurons, epithelial cells, immune cells, and endocrine cells, glucocorticoids can affect both gut and brain functions through multiple pathways including neural, metabolic, immunological, and endocrine pathways. Prolonged stress can induce the HPA axis dysregulation. In fact, it has been observed that increased cortisol is associated with cognitive decline and increased AD risk, with elevated cortisol in dementia patients involving interactions between inflammation, neurotransmitters, and oxidative stress.

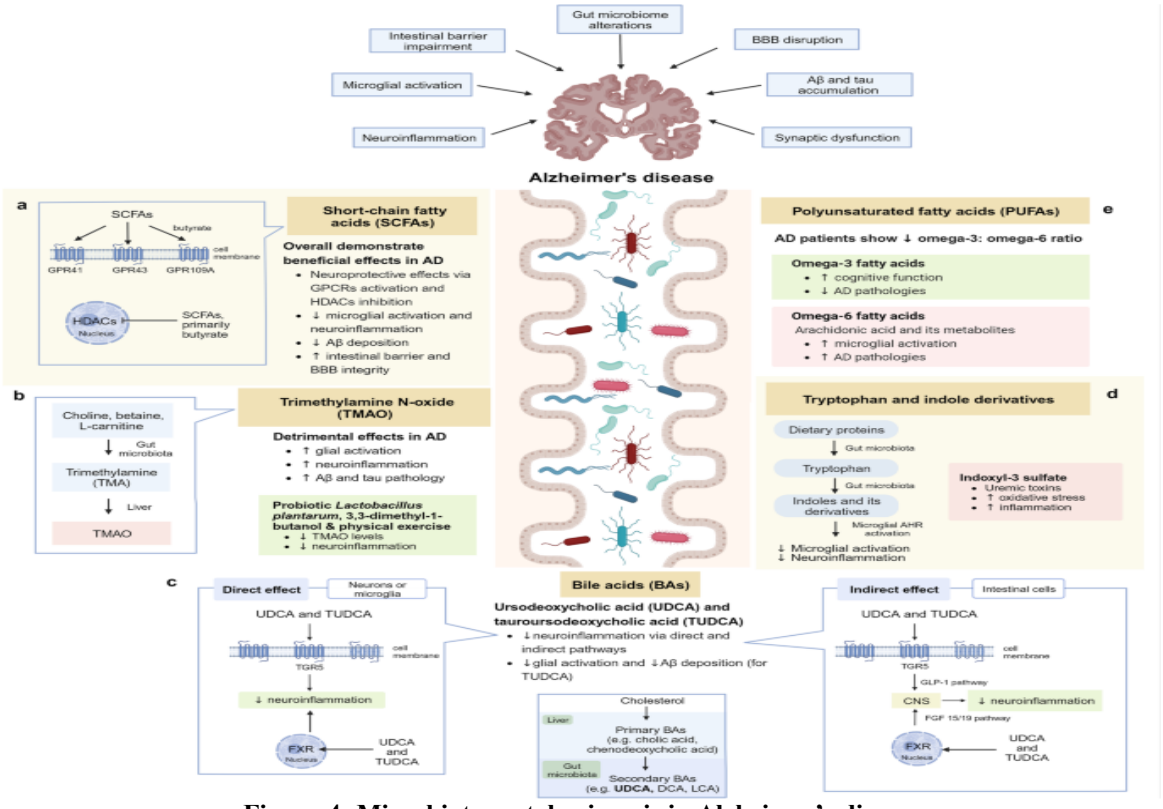

Figure-4: Microbiota–gut–brain axis in Alzheimer's disease

a Short-chain fatty acids (SCFAs) exert their neuroprotective effects by acting as endogenous ligands for G-protein-coupled receptors (GPCRs) and modulating gene expression by inhibiting histone deacetylases (HDACs). b Trimethylamine N-oxide (TMAO) promotes microglial activation, neuroinflammation, Aβ and tau patho logy. c Neuroprotective bile acids (BAs), including UDCA and TUDCA, inhibit neuro inflammation via direct and indirect pathways.

In the direct pathway, UDCA and TUDCA activate the nuclear receptor Farnesoid X receptor (FXR) and membrane receptor Takeda G-protein-coupled receptor 5 (TGR5) found in microglia and neurons. In the indirect pathway, UDCA and TUDCA provide signals to the central nervous system indirectly via intestinal TGR5-dependent glucagon-like peptide-1 (GLP-1) pathway and intestinal FXR-dependent fibroblast growth factor 15 or 19 (FGF15/19) pathway. d Tryptophan and indole derivatives activate microglial aryl hydrocarbon receptor (AHR) signaling to inhibit microglial activation and neuro inflammation.

e Polyunsaturated fatty acids (PUFAs): omega-3 fatty acids exhibit neuroprotective effects in Alzheimer's disease, whereas omega-6 fatty acid arachidonic acid and its pro-inflammatory metabolites induce microglial activation[1].

Table 1: From Bench to Clinic: The Emerging Role of Gut Microbiota in Neurodegenerative diseases and its key features:

Neurodegenerative Condition	Role of Gut Microbiota & Features
Alzheimer's disease (AD)	AD is the most common cause of dementia worldwide. AD is a multifactorial disorder with most cases being sporadic and only 5% of cases are early-onset familial AD. The classic neuropathological hallmarks of AD consist of amyloid-b (Ab) peptides for plaques and tau for tangles. Drug search efforts have focused on reducing Ab load in the brains of patients with AD; however, these treatments have failed in slowing mild cognitive impairment or dementia in AD. Studies have reported that gut microbiota is altered in AD. When AD patients were compared with healthy controls, AD patients exhibited diverse microbiota, an increased abundance of Bacteroidetes, and a reduced abundance of Firmicutes, Proteobacteria, and Actinobacteria. Moreover, the composition of the gut microbiota of SAPM8 mice, which exhibited learning and cognitive impairment similar to AD patients, revealed conspicuous character divergence compared with that of the healthy control; the correlation density and clustering operational taxonomic unit of gut microbiota decreased.
Amyotrophic lateral sclerosis (ALS)	ALS is a rare neurodegenerative disorder that affects motor neurons that extend from the brain to the spinal cord and to muscles throughout the body. Mutations in the SOD1 gene have been implicated in some cases of familial ALS. There is no treatment that reverses the disease and approved drugs can only slower the progression and ameliorate the symptoms.
Huntington's disease (HD)	HD is a genetic neurodegenerative disorder with an autosomal dominance inheritance, caused by the expansion of the trinucleotide (CAG) tandem repeat in the huntingtin (HTT) gene, encoding an expanded polyglutamine tract in the huntingtin protein. There are no disease-modifying therapies so far and the progression of the disease is 15 years from diagnosis to death. The symptomatology is complex with the presence of progressive cognitive, psychiatric, and motor impairments. A recent study compared the gut microbiota in an HD mouse model with that in wild-type mice and reported an increase in the abundance of Bacteroidales and Lactobacillales and a decrease in the abundance of Clostridiales in a male HD mouse model. By contrast, an increase in the abundance of Coriobacteriales, Erysipelotrichales, Bacteroidales, and Burkholderiale and a decrease in the abundance of Clostridiales were observed in female HD mice. Furthermore, male HD mice showed higher microbial diversity than both female and wildtype mice. Another study showed the decreased levels of myelin-related proteins and mature oligodendrocytes in the prefrontal cortex in microbiota-deficient mice, which led to reduced callosal myelination and white matter plasticity; the study revealed the effect of the lack of microbiota in aggravating internal HD phenotypes.
Multiple sclerosis (MS)	MS is considered an autoimmune disease that affects the central nervous system (CNS) including brain and spinal cord cells. Here, autoreactive T-cells enter the CNS from the peripheral circulation and induce an inflammatory cascade leading to demyelination. There is no cure for MS. However, FDA-approved medications alleviate exacerbations and accelerate recovery.

	Recent studies have shown that internal gut microbiota significantly effects MS and can be affected by environmental factors. The 16S rRNA sequencing of intestinal microbiota showed a high abundance of the phylum Firmicutes and lower abundance of the phylum Bacteroidetes in patients with MS than those in healthy controls. The increased abundance of Euryachaeota and Akkermansia has been observed in untreated patients with MS compared with that in healthy controls. Other studies have pointed out specifically that the decreased abundance of Prevotella in patients with RRMS can increase the disease activity. The reduction in Clostridium abundance in patients with RRMS, leading to a decreased level of SCFA secretion, was also observed in a study.
Parkinson's disease (PD)	PD is the second most common neurodegenerative disorder after AD. The cause of PD is not known, but several genetic and environmental risk factors have been shown to be associated with disease etiology. PD is characterized by classic motor symptoms and the neurodegeneration of dopaminergic neurons of the substantia nigra and reduction of dopaminergic content in the striatum. Another pathological hallmark is the accumulation of aggregates of a-synuclein, in the form of Lewy bodies and Lewy neuritis. Recent findings have shown that gut microbiota is closely related to PD and causes changes in microbe diversity and metabolites. In several case–control studies, an increasing abundance of Lactobacillaceae, Barnesiellaceae, and Enterococcacea was observed and a decreasing abundance of Clostridium coccoides, Bacteroides fragilis, and Prevotellaceae have been observed in PD patients compared with those in healthy controls.

Microbial–host metabolism interactions in the neurodegenerative disorders:

γ SCFAs The gut microbiota was shown to influence the metabolism of several neuroactive compounds that have been implicated in neurodegenerative disorders, including SCFAs [14].

The contribution of SCFAs to neurodegenerative conditions in clinical settings remains relatively unexplored with only a few human studies examining this relationship. For instance, in PD, individuals' fecal SCFAs concentrations seem to be lower compared with those of healthy controls [15], which may reflect the decrease in SCFA-producing bacteria (i.e. Faecalibacterium prausnitzii) in their gut microbiota [16]. In MS patients, the concentration of SCFAs producers is depleted in comparison to that of healthy individuals [17]. In line with this, the levels of circulating SCFAs are also lower [18]. A recent study demonstrated that individuals with MS have fewer species and lower levels of genes involved in butyrate production [19]. However, compared with healthy controls, MS patients have increased acetate levels, which correlated with greater disability and increased T helper 17 (TH17) cells [20]. The therapeutic potential of SCFAs to MS was also investigated in a cohort of 300 MS patients and it was demonstrated that treatment with propionate for 14 days was able to restore regulatory T-cell (Treg)/TH17 cells imbalance, normalize Tregs mitochondrial respiration, and improve long-term clinical symptoms [21]. These proof-of-concept studies strengthen the link between the gut microbiota and neurological diseases and highlight the potential use of microbial-based therapies in the management of neurodegenerative disorders.

Table-2: Gut Microbiota involved in Neurodegenerative Disease:

Bacterial genus	Possible involvements	Related neurodegenerative diseases
Escherichia, Pseudomonas, Staphylococcus, Streptococcus, Bacillus, Mycobacteria, Citrobacter, Klebsiella, Salmonella	Bacterial amyloid, FapCs. Translocate across BBB through GBA	Alzheimer's disease
Lactobacillus	GABA, Balance the regulation of cortical excitability and neural excitation-inhibition	Alzheimer's disease
Bifidobacterium	GABA, Balance the regulation of cortical excitability and neural excitation-inhibition	Alzheimer's disease
Proteobacteria, Bacteroidetes, Firmicutes, Actinobacteria,	Unknown	Alzheimer's disease

Lachnospiracea		
Roseburia, Faecalibacterium	Can produce SCFAs	Parkinson's disease
Pseudomonas	Fap. change of a-synuclein	Parkinson's disease
Enterobacteriaceae	Curli, a-synuclein aggregation	Parkinson's disease
Clostridium coccoides, Bacteroides fragilis, Prevotellaceae	Unknown	Parkinson's disease
Hydrogen-product bacteria	Reduced dopaminergic loss	Parkinson's disease
Coriobacteriales, Erysipelotrichales, Bacteroidales Burkholderiale	Unknown	Huntingdon disease
Clostridium	Decrease level of SCFA secretion	Multiple sclerosis
Firmicutes, Bacteroidetes, Prevotella	Unknown	Multiple sclerosis

In ALS, the abundance of SCFAs producers in the fecal microbiota is also reduced; however, this does not result in decreased fecal SCFAs concentrations. These discrepancies may be due to genetic heterogeneity of the subjects or differences in dietary habits. Thus, future studies should consider the role of host genetics and diets when investigating microbial–host metabolism interactions. Mechanistic insights towards understanding how SCFAs participate in neurodegenerative disorders are coming from in vivo animal studies. SCFA concentrations are altered in animal models of AD induced by injection of Ab [22] and are restored following the administration of Bifidobacterium breve A1—a bacterium that is known to produce SCFAs.

One important mechanism by which SCFAs seem to induce neuroprotection is via epigenetic modulation. Sodium butyrate improved motor behavior and altered global H3 histone acetylation and BDNF levels in the neurotoxin-based 6-hydroxidopamine (6-OHDA) model of PD. Similar effects were observed in mice administered with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxic compound known to induce dopaminergic neurodegeneration and PD model [23].

In the G93A mouse model of ALS, treatment with butyrate restored alterations in the gut microbiota composition and intestinal barrier deficits, decreased SOD1G93A protein aggregation in the intestine, and prolonged mice lifespan [24]. The influence of SCFAs in HD is less explored; however, administration of exogenous phenylbutyrate also induced neuroprotection and increased survival in the N171-82Q transgenic mouse model of HD via regulation of epigenetic markers [25]. SCFAs were also shown to modulate neuroinflammation and protein aggregation in animal models of neurodegenerative diseases. For example, SCFAs regulate motor deficits in the Thy1-a-Syn transgenic mouse model of PD via microglia activation and a-syn aggregation [26].

Further, SCFAs influence Ab plaque formation and the microglial transcriptomic profile, including upregulation of apolipoprotein E in a GF amyloidosis mouse model (APPPS1) relevant to AD. Acetate was also shown to affect microglial metabolism, function, and mitochondria number in the 5xFAD mice model of AD, which is based on the accumulation of high levels of neuronal Ab42.

These studies show that SCFAs can modulate disease or induce neuroprotection in different animal models of neurodegenerative conditions. Identification of cell-type-specific effects of microbial metabolites is essential for accessing the contribution of the gut microbiota to cell vulnerability to neurodegeneration [27].

γ Tryptophan metabolism:

Several Trp-derived metabolites have been shown to regulate inflammation, with implications for autoimmune and neurodegenerative disorders. One of the largest integrated metabolomics-metagenomic studies revealed that plasma indolelactate, indolepropionate, and its producing bacteria are lower in patients with MS compared with controls. In the EAE mouse model, dietary Trp is required for induction of autoimmune neuroinflammation as mice fed a free-Trp diet have decreased numbers of circulating myelin oligodendrocyte glycoprotein (MOG) 35–55 reactive $CD4^+$ T-cells—a finding that was dependent on the presence of an intact gut microbiota as antibiotics-treated mice do not exhibit the phenotype [28].

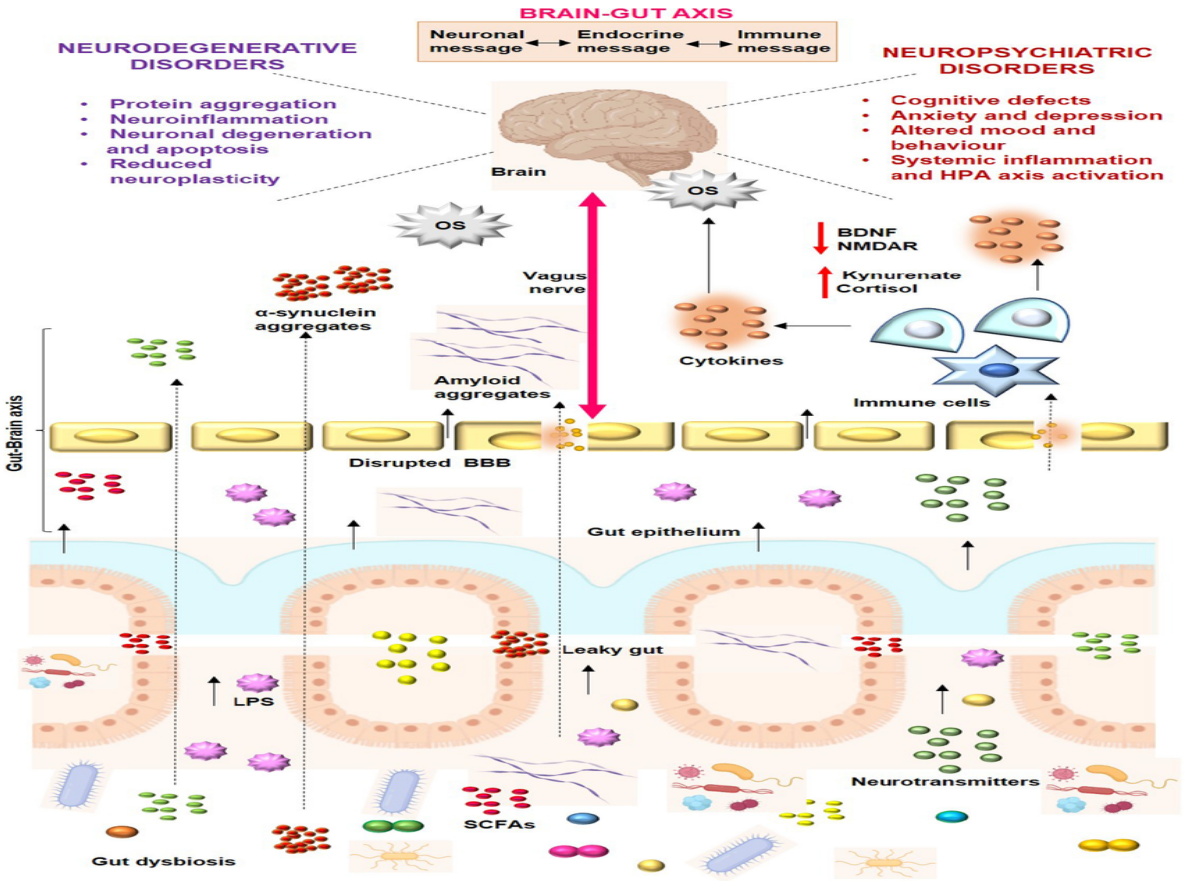

Figure 5: Relevance of brain-gut microbiota axis in neurodegenerative and neuropsychiatric disorders: the gut microbiota impacts brain functioning via three different mechanisms—neuronal, endocrine, and immune messages

The gut microbiota secrete various factors including neurotransmitters, hormones, amino acids, lipopolysaccharides (LPS), and anti-inflammatory molecules like SCAFs. All these components affect brain metabolism by passing through the circulation. In neuropathological conditions such as protein aggregation, stress, anxiety, and depression, the hypothalamic neurons trigger the release of cortisol hormone and disturbs the permeability of the gut epithelium and blood–brain barrier. Gut dysbiosis leads to the activation of various peripheral immune responses and release of inflammatory cytokines. All these factors negatively affect brain homeostasis accompanied with increase in reactive oxygen species and protein aggregation [1] (for instance, amyloid-beta fibril formation in Alzheimer's disease and alpha-synuclein aggregation in Parkinson's disease).

In a separate study using the EAE mouse model, supplementation with indoxyl-3-sulfate, a microbial metabolite produced by dietary Trp, activated microglia and elevated transforming growth factor alpha (TGF-α) and vascular endothelial growth factor beta (VEGF-β) production, which in turn modulated astrocyte activity and CNS inflammation through a mechanism mediated by the aryl hydrocarbon receptor (AhR) [29]. AhRs signaling is largely involved in peripheral immune system activation, maintenance of the gut barrier integrity, and host defense against pathogens and inflammatory insults. In the CNS, the AhR pathway impacts microglia and the function of astrocytes, and participates in adult neurogenesis [30].

Alterations in the Trp metabolism have been linked to cognitive decline in AD patients [31]. A recent study that investigated alterations in fecal metabolites showed a decrease in hydroxy tryptophan and DL-5- methoxytryptophan in AD patients' samples in comparison to healthy controls' samples [32]. In the same study, the abundance of indole derivatives that participate in AhR signaling were also decreased in the AD fecal metabolome whereas kynurenine levels were unchanged [33]. In line, indolamine 2,3-dioxygenase (IDO), a rate-limiting enzyme in the conversion of Trp to kynurenine, is increased in AD and inhibition of this IDO ameliorated anxiety and depression-like behaviors in 3xTg-AD mice, a triple-transgenic mouse line that exhibit both Ab and tau pathology [34]. Similarly, Trp metabolism is altered in PD individuals and in animal models of disease [35]. Analysis of a publicly available microbiota data set of PD patients and healthy

controls revealed an increase in indole-producing bacteria (i.e. Akkermansia, Alistipes, and Porphyromonas) in PD patients [36]. In a rat model of PD induced by rotenone, dietary Trp improved motor deficits and attenuated neurodegeneration and neuroinflammation via AhR activation. Thus, the gut microbiota effect on Trp metabolism may have a significant impact on neurodegenerative disorders and warrants further investigation.

The Gut Microbiota in Potential Treatment Strategies:

There are two suggested approaches to upcoming treatments that target the intestinal flora. The first is the direct eradication or alteration of certain microbes, similar to antibiotic therapy for peptic ulcers caused by H. pylori. The second takes a more comprehensive approach, using profiling techniques such as metabolomics to classify illnesses according to the gut microbiota structures associated with clinical symptoms [37]. To effectively treat the gut microbiota, a combination of antibiotics, probiotics, prebiotics, and maybe laxatives might be utilized. This has the potential to help treat several illnesses, including diabetes. Drug discovery is made possible by culture-independent metagenomic technology, which suggests that the gut microbiome itself may include potential therapeutics. The discovery of genes encoding bioactive chemicals from commensal microbiota is made easier by high-throughput DNA sequencing and bioinformatics techniques, opening up new avenues for medication development [38].

It has been discovered that FMT from normal mice inhibits neuroinflammation and the activation of the glial cells, protecting them against PD caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In contrast, characteristic motor impairments are worsened when the microbiota from PD patients is colonized in mice overexpressing synuclein (Syn) as opposed to when microbiota from healthy human donors is used. In a therapeutic setting, a PD patient's extreme constipation and tremors were successfully reduced using FMT therapy [39]. The gut microbiome may be structurally repaired with the transplantation of microbiota containing Faecalibacterium prausnitzii. Interestingly, compared to control individuals, PD patients had a noticeably lower amount of F. prausnitzii, suggesting a possible relation.

The presence of F. prausnitzii might be used as a biomarker for analysis or diagnosis to determine whether FMT is successful [40]. Furthermore, probiotics and/or prebiotics can be used to prevent and treat neurodegenerative illnesses. The use of prebiotics and/or probiotics in the gut microbiota has demonstrated potential in the management of ALS, indicating that adjusting the gut microbiota may be a novel approach to treating ALS [41]. Because of its complexity, the role of the gut microbiota in diseases must be understood in the larger framework of systems biology. Although the microbiome has a role in diseases, it is rarely the sole cause. Comprehending the proportional contribution of the gut microbiota to conditions requires large-scale, well-phenotyped cohort studies employing multi-omics techniques. Drug metabolism, side effects, and the treatment response can all be influenced by several factors. It is simplistic to categorize entire genera as advantageous or detrimental; instead, individual microbiomes should be profiled using higher-resolution approaches. For precision medicine, microbial functions may be more important than taxonomic abundances. Based on improved mechanistic knowledge, therapies should target missing functions and identify various functional challenges among different patients [42]. Table 3 summarizes the impact of different gut microbial species on physiology, emphasizing their involvement in causing or alleviating inflammation and other physiological processes.

Table 3. Myriad Gut Microbiota Impacts:

Bacterial Species	Impact On Human Physiology
Bifidobacterium longum	Anti-inflammatory Reduced amyloid aggregation
Clostridium perfringens type B	Produces toxins Damages tissues and nerves
Escherichia coli	Protein misfolding through molecular mimicry Pro-inflammatory
Lactobacilli acidophilus	Anti-inflammatory Strengthen gut barrier Produce beneficial SCFAs
Campylobacter concisus	Pro-inflammatory Produces endotoxins Protein misfolding through molecular mimicry Disrupts GBA communication
Akkermansia muciniphila	Anti-inflammatory Gut barrier fortification

	Promotes neurotransmitter levels
Dorea formicigenerans	Stimulates IFNγ Metabolizes sialic acid Degrades mucin
Acinetobacter calcoaceticus	Stimulates pro-inflammatory cytokines Depresses regulatory CD4 T cells
Bacteroides fragilis	Pro-inflammatory Protein misfolding through molecular mimicry Leaky gut
Eubacterium rectale	Anti-inflammatory Produces beneficial SCFAs

Reasoning Queries and Ahead Direction:

The nature of cellular and molecular pathologies underlying gut dysfunction: The persistence of gut dysfunction while the ENS structure remains intact in some NDs suggests that homeostatic mechanisms still cause profound neurochemical and molecular changes in ENS neurons. While continual neurogenesis might repair ENS neuronal loss that is elevated in the gut of individuals with NDs, this should be tested by performing BrdU-labeling experiments and apoptosis assays to calculate the rate of neuronal turnover. In addition, alterations to ENS and GBA neurons at the neurochemical and molecular levels should be studied using immunohistochemical, physiological, and newer single-cell transcriptomic techniques.

Mechanistic role of microbiota in causing or reverting NDs: Although the microbiota play a notable role in NDs, their exact nature and mechanistic contribution are unknown. Although the presence of gut bacteria in mutant mice aid in the progression of some NDs, specific bacteria or microbial communities may play a beneficial role in arresting or even reverting other NDs.

A better understanding of their role will require mechanistic insights into how microbiota regulate the ENS and the associated MMs maintain gut function, as well as how they stimulate the GBA in the context of ND mouse models.

Conclusion

Nourishment is a natural and physiological need to obtain energy and seek food from the environment for a good quality life. The gut-brain axis comprises a natural and highly organized neuroendocrine circuit between the brain's hunger-satiety and dopaminergic reward systems in conjunction with the gut microbiota, which regulates our emotions and food-decision making.

However, genetic variations, altered physiology and the consumption of fad diets may lead obesity and other associated chronic co-morbidities. So in order to maintain the balanced physiological process and quality life we have to focus on personalized medicine and genome-based strategies. Thus, gastroenterologist that have to prevent and treat GI disorders associated with obesity and negative emotions an integrated and well-known approach based on the concept of the neuroendocronological circuit (genes, emotions and gut microbiota) interactions should be monitored. Gut microbiota influences physiological brain functions through modulating the immune system, direct neural signaling, and activating the humoral pathway by microbial molecules and some unknown potential pathways. Considerable attention has been paid toward elucidating the unknown mechanism and influence factors; therefore, direct intervention of ND pathophysiology by gut microbiota should be reconsidered. Further studies clinical cum experimental on these mysteries are required so that better understanding and revealing may light to the day regarding the underlying mechanism.

References

1. Jian Sheng Loh, Wen Qi Mak, Li Kar Stella Tan, Chu Xin Ng, Hong Hao Chan, Shiau Hueh Yeow, Jhi Biau Foo, Yong Sze Ong, Chee Wun How & Kooi Yeong Khaw, Signal Transduction and Targeted Therapy: Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases; British Journal of Cancer: Volume 9, Article number: 37 (2024).
2. Geng, Z.H.; Zhu, Y.; Li, Q.L.; Zhao, C.; Zhou, P.H. Enteric Nervous System: The Bridge Between the Gut Microbiota and Neurological Disorders. Front. Aging Neurosci. 2022, 14, 810483. [Google Scholar] [CrossRef] [Pub Med].
3. Furness, J.B. The Enteric Nervous System and Neurogastroenterology. Nat. Rev. Gastro enterol. Hepatol. 2012, 9, 286–294. [Google Scholar] [CrossRef].
4. Annahazi, A.; Schemann, M. The Enteric Nervous System: "A Little Brain in the Gut". Neuroforum 2020, 26, 31–42. [Google Scholar] [CrossRef].
5. Rao, M.; Gershon, M.D. The Bowel and beyond: The Enteric Nervous System in Neurological Disorders. Nat. Rev. Gastro enterol. Hepatol. 2016, 13, 517–528. [Google Scholar] [CrossRef] [PubMed].

6. Brun, P.; Gobbo, S.; Caputi, V.; Spagnol, L.; Schirato, G.; Pasqualin, M.; Levorato, E.; Palù, G.; Giron, M.C.; Castagliuolo, I. Toll like Receptor-2 Regulates Production of Glial-Derived Neurotrophic Factors in Murine Intestinal Smooth Muscle Cells. Mol. Cell. Neurosci. 2015, 68, 24–35. [Google Scholar] [CrossRef].
7. Caputi, V.; Marsilio, I.; Filpa, V.; Cerantola, S.; Orso, G.; Bistoletti, M.; Paccagnella, N.; De Martin, S.; Montopoli, M.; Dall'Acqua, S.; et al. Antibiotic-Induced Dysbiosis of the Microbiota Impairs Gut Neuromuscular Function in Juvenile Mice. Br. J. Pharmacol. 2017, 174, 3623–3639. [Google Scholar] [CrossRef].
8. Kabouridis, P.S.; Lasrado, R.; McCallum, S.; Chng, S.H.; Snippert, H.J.; Clevers, H.; Pettersson, S.; Pachnis, V. Microbiota Controls the Homeostasis of Glial Cells in the Gut Lamina Propria. Neuron 2015, 85, 289–295. [Google Scholar] [CrossRef].
9. Yano, J.M.; Yu, K.; Donaldson, G.P.; Shastri, G.G.; Ann, P.; Ma, L.; Nagler, C.R.; Ismagilov, R.F.; Mazmanian, S.K.; Hsiao, E.Y. Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell 2015, 161, 264–276. [Google Scholar] [CrossRef].
10. Rolig, A.S.; Mittge, E.K.; Ganz, J.; Troll, J.V.; Melancon, E.; Wiles, T.J.; Alligood, K.; Stephens, W.Z.; Eisen, J.S.; Guillemin, K. The Enteric Nervous System Promotes Intestinal Health by Constraining Microbiota Compo sition. PLoS Biol. 2017, 15, e2000689. [Google Scholar] [CrossRef].
11. Chalazonitis, A.; Rao, M. Enteric Nervous System Manifestations of Neurodegenerative Disease. Brain Res. 2018, 1693, 207–213. [Google Scholar] [CrossRef] [PubMed].
12. Smith, S.M.; Vale, W.W. The Role of the Hypothalamic-Pituitary-Adrenal Axis in Neuroendocrine Responses to Stress. Dialogues Clin. Neurosci. 2006, 8, 383–395. [Google Scholar] [CrossRef] [PubMed].
13. Sudo, N. The Hypothalamic-Pituitary-Adrenal Axis and Gut Microbiota: A Target for Dietary Intervention? In The Gut-Brain Axis Dietary, Probiotic, and Prebiotic Interventions on the Microbiota; Elsevier Inc.: Amsterdam, the Netherlands, 2016; pp. 293–304. [Google Scholar] [CrossRef].
14. Ouanes, S.; Popp, J. High Cortisol and the Risk of Dementia and Alzheimer's disease: A Review of the Literature. Front. Aging Neurosci. 2019, 11, 43. [Google Scholar] [CrossRef] [PubMed].
15. Needham BD, Kaddurah-Daouk R, Mazmanian SK. Gut microbial molecules in behavioural and neurodegenerative conditions. Nat Rev Neurosci 2020; 21:717–31.
16. Unger MM, Spiegel J, Dillmann K-U et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord 2016; 32:66–72.
17. Aho VTE, Houser MC, Pereira PAB et al. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. Mol Neurodegener 2021; 16:6.
18. Keshavarzian A, Green SJ, Engen PA et al. Colonic bacterial composition in Parkinson's disease. Mov Disord 2015; 30: 1351–60.
19. Duscha A, Gisevius B, Hirschberg S et al. Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism. Cell 2020; 180:1067–80.e16.
20. Olsson A, Gustavsen S, Nguyen TD et al. Serum short-chain fatty acids and associations with inflammation in newly diagnosed patients with multiple sclerosis and healthy controls. Front Immunol 2021; 12:1560.
21. Levi I, Gurevich M, Perlman G et al. Potential role of indolelactate and butyrate in multiple sclerosis revealed by integrated microbiome-metabolome analysis. Cell Rep Med 2021; 2:100246.
22. Acetate correlates with disability and immune response in multiple sclerosis. PeerJ 2020; 8:e10220.
23. Niccolai E, Di Pilato V, Nannini G et al. The gut microbiotaimmunity axis in ALS: a role in deciphering disease heterogeneity? Bio medicines 2021; 9:753.
24. Kobayashi Y, Sugahara H, Shimada K et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci Rep 2017; 7: 13510.
25. Hou Y, Li X, Liu C et al. Neuroprotective effects of shortchain fatty acids in MPTP induced mice model of Parkinson's disease. Exp Gerontol 2021; 150:111376.
26. Zhang Y, Wu S, Yi J et al. Target intestinal microbiota to alleviate disease progression in amyotrophic lateral sclerosis. Clin Ther 2017; 39:322–36.
27. Gardian G, Browne SE, Choi D-K et al. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J Bio Chem 2005; 280:556–63.
28. Sampson TR, Debelius JW, Thron T et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 2016; 167:1469–80.e12.
29. Colombo AV, Sadler RK, Llovera G et al. Microbiota-derived short chain fatty acids

modulate microglia and promote Ab plaque deposition. Elife 2021; 10:e59826.
30. Sonner JK, Keil M, Falk-Paulsen M et al. Dietary tryptophan links encephalogenicity of autoreactive T cells with gut microbial ecology. Nat Commun 2019; 10:4877.
31. Rothhammer V, Borucki DM, Tjon EC et al. Microglial control of astrocytes in response to microbial metabolites. Nature 2018; 557:724–8.
32. Scott SA, Fu J, Chang PV. Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. Proc Natl Acad Sci USA 2020; 117:19376–87.
33. Porter RJ, Lunn BS, Walker LL et al. Cognitive deficit induced by acute tryptophan depletion in patients with Alzheimers disease. Am J Psychiatry 2000; 157:638–40.
34. Wu L, Han Y, Zheng Z et al. altered gut microbial metabolites in amnestic mild cognitive impairment and Alzheimer's disease: signals in host–microbe interplay. Nutrients 2021; 13: 228.
35. Fertan E, Stover KRJ, Brant MG et al. Effects of the novel IDO inhibitor DWG-1036 on the behavior of male and female 3xTg-AD mice. Front Pharmacol 2019; 10:1044.
36. Venkatesan D, Iyer M, Narayanasamy A et al. Kynurenine pathway in Parkinson's disease: an update. eNeurologicalSci 2020;21:100270.
37. Chen, Y.; Liao, X.; Li, Y.; Cao, H.; Zhang, F.; Fei, B.; Bao, C.; Cao, H.; Mao, Y.; Chen, X.; et al. Effects of prebiotic supplement on gut microbiota, drug bioavailability, and adverse effects in patients with colorectal cancer at different primary tumor locations receiving chemotherapy: Study protocol for a randomized clinical trial. Trials 2023, 24, 268. [CrossRef] [PubMed].
38. Jia, W.; Li, H.; Zhao, L.; Nicholson, J.K. Gut microbiota: A potential new territory for drug targeting. Nat. Rev. Drug Discov. 2008, 7, 123–129. [CrossRef] [PubMed].
39. Huang, H.; Xu, H.; Luo, Q.; He, J.; Li, M.; Chen, H.; Tang, W.; Nie, Y.; Zhou, Y. Fecal microbiota transplantation to treat Parkinson's disease with constipation: A case report. Medicine 2019, 98, 16163. [CrossRef].
40. Grün, D.; Zimmer, V.C.; Kauffmann, J.; Spiegel, J.; Dillmann, U.; Schwiertz, A.; Faßbender, K.; Fousse, M.; Unger, M.M. Impact of oral COMT-inhibitors on gut microbiota and short chain fatty acids in Parkinson's disease. Park. Relat. Disord. 2020, 70, 20–22. [CrossRef] [PubMed].
41. Casani-Cubel, J.; Benlloch, M.; Sanchis-Sanchis, C.E.; Marin, R.; Lajara-Romance, J.M.; de la Rubia Orti, J.E. The Impact of Microbiota on the Pathogenesis of Amyotrophic Lateral Sclerosis and the Possible Benefits of Polyphenols. An Overview. Metabolites 2021, 11, 120. [CrossRef] [PubMed].
42. Schupack, D.A.; Mars, R.A.T.; Voelker, D.H.; Abeykoon, J.P.; Kashyap, P.C. The promise of the gut microbiome as part of individualized treatment strategies. Nat. Rev. Gastroenterol. Hepatol. 2022, 19, 7–25. [CrossRef]