Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: Tales of a vicious cycle

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Abstract

The human microbiota comprises trillions of symbiotic microorganisms and is involved in regulating gastrointestinal (GI), immune, nervous system and metabolic homeostasis. Recent observations suggest a bidirectional communication between the gut microbiota and the brain via immune, circulatory and neural pathways, termed the Gut-Brain Axis (GBA). Alterations in gut microbiota composition, such as seen with an increased number of pathobionts and a decreased number of symbionts, termed gut dysbiosis or microbial intestinal dysbiosis, plays a prominent role in the pathogenesis of central nervous system (CNS)-related disorders. Clinical reports confirm that GI symptoms often precede neurological symptoms several years before the development of neurodegenerative diseases (NDDs). Pathologically, gut dysbiosis disrupts the integrity of the intestinal barrier leading to ingress of pathobionts and toxic metabolites into the systemic circulation causing GBA dysregulation. Subsequently, chronic neuroinflammation via dysregulated immune activation triggers the accumulation of neurotoxic misfolded proteins in and around CNS cells resulting in neuronal death. Emerging evidence links gut dysbiosis to the aggravation and/or spread of proteinopathies from the peripheral nervous system to the CNS and defective autophagy-mediated proteinopathies. This review summarizes the current understanding of the role of gut microbiota in NDDs, and highlights a vicious cycle of gut dysbiosis, immune-mediated chronic neuroinflammation, impaired autophagy and proteinopathies, which contributes to the development of neurodegeneration in Alzheimer's disease, Parkinson's disease, Huntington’s disease, multiple sclerosis, amyotrophic lateral sclerosis and frontotemporal lobar degeneration. We also discuss novel therapeutic strategies targeting the modulation of gut dysbiosis through prebiotics, probiotics, synbiotics or dietary interventions, and faecal microbial transplantation (FMT) in the management of NDDs.

Key words: Gut microbiota, dysbiosis, proteinopathies, autophagy, neuroinflammation, neurodegenerative diseases

Abbreviations

5-HT: 5-hydroxytryptamine; 6-OHDA: 6-hydroxy dopamine; AD: Alzheimer's disease; ADLP^{APT}: Transgenic AD mice with Aβ plagues, neurofibrillary tangles, reactive gliosis in the brain and gut dysbiosis; ALS: Amyotrophic lateral sclerosis; APP: amyloid precursor protein; ASD: Autism spectrum disorder; Atg5: autophagy-related 5; Aβ: β-amyloid; BBB: brain-blood barrier; BDNF: brain derived neurotrophic factor; BMAA: β-N-methylamino-L-alanine; CCK: cholecystokinin; CD32: Cluster of differentiation 32; CD68: Cluster of differentiation 68; CLDN2: claudin 2; CNS: central nervous system; CRP: C-reactive protein; EECs: enteroendocrine cells; ENS: enteric nervous system; ER: endoplasmic reticulum; FMT: Faecal microbial transplantation; GABA: gamma aminobutyric acid; GBA: Gut-Brain Axis; GF: Germ-free; GI: gastrointestinal; GM: Gut microbiota; GOS: galacto-oligosaccharides; HPA: hypothalamic-pituitary adrenal; IBS: irritable bowel syndrome; IECs: intestinal epithelial cells; IFN-γ: Interferon-γ; IL-1β: Interleukin-1β; IL-6: Interleukin-6; LPS: Lipopolysaccharide; MAMPs: microbe-associated molecular patterns; MS: multiple sclerosis; NDDs: neurodegenerative diseases; NF-kB: Natural factor-kappa B; OS: Oxidative stress; PAMPs: Pathogen-associated molecular patterns; PAP mice: APP/PS1 transgenic mice mimicking AD with severe gut dysbiosis; PD: Parkinson's disease; PRRs: pattern recognition receptors; PS1: presenilin 1; RNS: reactive nitrogen species; ROS: Reactive oxygen species; SCFAs: Short chain fatty acids; SOCS3: Suppressor of cytokine signaling 3; SPF: Specific pathogen free; TLR4: toll-like receptor-4; TNF-α: Tumour necrosis factor-α; WT: wild-type; αSyn: α-Synuclein.

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1. Introduction

The human microbiota is a complex, dynamic and symbiotic ecosystem comprising trillions of host-specific microorganisms such as bacteria, viruses, fungi, and protozoa living in symbiosis (Borre et al., 2014; Sender et al., 2016). The **gut microbiota** refers to the diverse variety of microorganisms co-evolved in the human gut (Donaldson et al., 2016; Zhu et al., 2013). These taxonomically diverse intestinal microbes are known to maintain host homeostasis by regulating digestive, immune, metabolic, and various neurological functions (Quigley, 2017; Sampson et al., 2016). The intestinal microbes are mainly involved in promoting the digestion and absorption of complex carbohydrates, producing vital energy sources such as short-chain fatty acids (SCFAs) (Bauer et al., 2016), regulating metabolism of essential substances (bile acids, sterols and drugs), synthesizing important vitamins such as vitamin B and K, maintaining the integrity of intestinal epithelial barrier (Dalile et al., 2019), competing with pathogens and preventing their colonization, and promoting the development and maturation of the immune system (Dinan and Cryan, 2017; Fung et al., 2017; Singh et al., 2016; Tilg et al., 2020).

Mounting evidence suggests that the gut and brains has a strong bidirectional communication, commonly termed the **gut-brain axis (GBA)** (Luan et al., 2019; Rosario et al., 2020)- through neural, endocrine and immune mechanisms (Carabotti et al., 2015; Mills et al., 2019; Rogers et al., 2016; Vogt et al., 2017). Two decades of GBA research suggests that the gut microbiota can be considered as a new vital organ (Guinane and Cotter, 2013), with a specific influence on neural development, cognition and behaviour (Moloney et al., 2014).

The imbalance in the number of microbes producing anti-inflammatory cytokines (anti-inflammatory taxa) and microbes producing pro-inflammatory cytokines (pro-inflammatory taxa) in the gut is termed **gut dysbiosis**, and may be a primary factor underlying various GI disorders such as irritable bowel syndrome (IBS), ulcerative colitis, and Crohn's disease

(Ballway and Song, 2021; Dinan et al., 2014; Kowalski and Mulak, 2019), through augmentation of lipopolysaccharides (LPS), pro-inflammatory cytokines, T helper cells and monocytes leading to increased intestinal (resulting in leaky gut syndrome) and brain-blood barrier (BBB) permeability via the GBA (Cho et al., 2019; Luan et al., 2019) **[Text Box-1]**.

Text Box-1

KEY DEFINITIONS

- **Gut microbiota (GM)** collectively refers to the 10^{13}–10^{14} of microorganisms comprising bacteria, viruses, fungi, and protozoans that colonize the GI tract [mouth, pharynx, larynx, oesophagus, stomach and intestines] of the human (Sender R et al., 2016).
- **Gut microbiome** defines both the composition and functional characteristics of GM (Wang HX and Wang YP, 2016).
- **Gut-Brain axis (GBA) or Microbiota-Gut-Brain (MGB)** axis is the term used for the complex bidirectional communication between the central nervous system (CNS) and GM of the enteric nervous system (ENS) (Sherwin E et al., 2016).
- **GBA pathways** refers to the neural, immune, endocrine, and metabolic signalling pathways involved in the dynamic crosstalk between the brain and GM (Quigley EMM, 2019).
- **Gut or microbial dysbiosis** refers to the alteration in the GM composition, specifically trending towards an increase in pro-inflammatory species (pathogenic bacteria or pathobionts) and decreased levels of anti-inflammatory species (beneficial bacteria or symbionts), along with altered levels of microbial metabolites and neuroactive molecules leading to dysregulated signalling via the GBA (Dinan and Cryan, 2017).

- **Prodromal phase** - Long interphase between the disease onset and appearance of clinical symptoms. In NDDs, the pathological proteins are detected in biopsy samples of patients.
- **Symptomatic phase** - Advanced stage of the disease with manifestations of the clinical symptoms.

Recent evidence demonstrates the pathogenic role of gut dysbiosis in a plethora of CNS-related diseases (Liang et al., 2018; Tremlett et al., 2016) ranging from neuropsychiatric disorders (Foster et al., 2017; Friedland and Chapman, 2017) such as depression, anxiety, and autism to NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal lobar degeneration, and neuro (auto) immune disorders including amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) (Chitnis and Weiner, 2017; Scheperjans et al., 2015). Extensive preclinical and clinical studies confirm that gut dysbiosis has a clear link to the etiopathology and pathophysiology of NDDs including AD, PD, Lewy body (LB) disease, ALS, frontotemporal lobar degeneration and prion disease (Bayer, 2015; Friedland, 2015; Luan et al., 2019) . Clinical data have shown that patients with NDDs and neuropsychiatric diseases commonly report GI dysfunction in the prodromal phase, several years before the symptomatic phase (Fung et al., 2017; Soto and Pritzkow, 2018). Generally, the central pathology of PD, AD, HD, MS, and AML is characterized by the deposition of aggregates of misfolded disease-specific neurotoxic proteins, which are commonly termed "Proteinopathies" (Bayer, 2015; Friedland, 2015). These misfolded protein conformations accumulate as small oligomers or large fibrillary aggregates, and are confined to specific anatomic brain regions, thus leading to specific clinical manifestations (Tremlett et al., 2017; Tyler Patterson and Grandhi, 2020). Further, detrimental activation of the innate and adaptive immune systems results in chronic neuroinflammation (Berer et al., 2011; Cryan and Dinan,

2012; Kikis et al., 2010) and impaired protein clearance or autophagy that alters brain morphology and physiology adding to clinical pathology (Caputi and Giron, 2018; Golde and Miller, 2009).

Gut dysbiosis mediated dysregulated autophagy affects gut barrier integrity and increases intestinal permeability, allowing the translocation of gut microbes, microbial-derived metabolites and microbe-associated molecular patterns (MAMPs) into the mesenteric lymphoid tissues, which causes neuroinflammatory reactions, and in turn, the progression and development of neurological disorders (Yan Wang et al., 2019). Further, dysregulated autophagy leads to disrupted clearance of polyubiquitinated protein aggregates in neurons and impairs endoplasmic reticulum (ER) homeostasis during stress, aging, and NDDs. These findings suggest that failure of the autophagic system to clear the misfolded proteins (Fitzgerald et al., 2019; König et al., 2016) is one of the main triggering factors for neuroinflammation, leading to neurodegeneration (Caputi and Giron, 2018). Moreover, gut dysbiosis triggers and/or amplifies aberrant immune-mediated chronic inflammation (Singh et al., 2016) that spreads from the systemic circulation to the brain, which further triggers protein misfolding as well as its aggregation, axonal damage and neuronal demyelination (Schwartz and Baruch, 2014; Wells et al., 2017).

Pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) primarily expressed in gut microorganisms (de Vos and de Vos, 2012), activate the innate immune system by binding to pattern recognition receptors (PRRs) (Lozupone et al., 2012). These PRRs are expressed by a variety of host immune cells including intestinal epithelial cells (IECs), enteroendocrine cells (EECs), and immune cells in peripheral blood as well as neurons and glial cells of the CNS and PNS (de Vos and de Vos, 2012; Mosca et al., 2016). Furthermore, gut dysbiosis-induced mitochondrial dysfunction in the CNS cells amplifies oxidative stress (OS) leading to neuronal inflammation. In contrast, misfolded

proteins and amyloid deposits, act as PAMPs and change the functions of the gut microbiota. The close interaction of gut-microbiota-OS-mitochondrial dysfunction and NDDs highlights the importance of GBA connections (Yan Wang et al., 2019). Neuropathological studies in AD and PD provide evidence that the gut microbiota is capable of influencing amyloid-β peptide (Aβ) development in AD (Kowalski and Mulak, 2019) and α-synuclein (αSyn) pathology in PD, respectively (Fitzgerald et al., 2019; Sampson et al., 2016). Specifically, gut dysbiosis has been reported to trigger gut barrier dysfunction, by inducing changes in tight junctions, mucous layers, intraepithelial lymphocytes, and secretion of immunoglobulin A (König et al., 2016; Wells et al., 2017). These changes lead to the aberrant activation of the innate and adaptive immune systems (Amor and Woodroofe, 2014; López-Valdés and Martínez-Coria, 2016), which induce chronic neuroinflammation, which leads to the aggregation and accumulation of misfolded proteins in the CNS cells (Chitnis and Weiner, 2017; Schwartz and Baruch, 2014). However, the complex connections between immune activation and impaired autophagy that leads to proteinopathies and the precise influence of the gut microbiota on the brain, still remains to be fully understood. This review discusses the pathophysiological correlation of gut dysbiosis with proteinopathies, impaired autophagy and immune dysregulation in NDDs including AD, PD, HD, ALS, MS and FLTD. Further, we discuss potential therapeutic interventions that may prevent the initiation, progression and relapse of NDDs by restoring gut eubiosis.

1.1. Bidirectional communication between the gut microbiota and brain

The human microbiota comprises more than 5000 strains of microbes with 1000 or more kinds of microflora (de Vos and de Vos, 2012; Lozupone et al., 2012). The gut microbiota includes

500–1,000 species of bacteria, reaching the maximum in the colon (Mosca et al., 2016; Rajilić-Stojanović and de Vos, 2014). More than 150 bacterial species that encode 150 times more genes than human genome reside in the gut microbiota. Each individual has at least 160 bacterial species and greater than 3 million microbial genes, with 3 distinct enterotypes comprising *Bacteroides, Prevotella, and Ruminococcus* genera (Arumugam et al., 2011). The gut microbiota in humans is comprised of four major phyla (*Bacteroidetes, Firmicutes, Proteobacteria,* and *Actinobacteria)* and two minor phyla (*Verrucomicrobia* and *Fusobacteria*) (Bäckhed, 2011; Qin et al., 2010). After birth, the sterile gut of the new born becomes colonized by microbes and is influenced by gestational age, mode of delivery and feeding (Dominguez-Bello et al., 2010; Karlsson et al., 2011), level of sanitation and exposure to antibiotics (Fouhy et al., 2012; Marques et al., 2010). By one to three years of age, gut microbiota colonization reaches that of the adult complex microbiome (Biasucci et al., 2010; Vaishampayan et al., 2010; Vallès et al., 2012). Extrinsic factors, including long-term dietary habit, lifestyle, infection, physical activity, and exposure to antibiotics, stress and early microbiota (David et al., 2014; Levy et al., 2017), and intrinsic factors such as genetic background, metabolism, immunity, and hormones, determine the composition of gut microbiota (Coman and Vodnar, 2020) **[Text Box-2]**.

Text Box-2

KEY DEFINITIONS

- **Commensals** are non-pathogenic bacteria that predominantly colonize the GI tract such as *Lactobacillus* species (*L. rhamnosus, L. acidophilus, L. plantarum* etc), Bifidobacterium (*B. bifidum*), *Enterococci, Propionobacteria* and *Peptostreptococci*. Commensals when beneficial to the host health are termed **symbionts**.
- **Pathobionts** define microbes with pathogenic potential like *Bacteriodes*, *Bacilli*, *Clostridia, Enterobacteria, Actenobacteria, Peptococci, Staphylococci, Streptococci* and yeasts etc. (Joshi et al., 2018).
- **Conversion** - Most microbes can shift from commensal to symbionts or pathobionts form depending on exposure to pathogen, antibiotics and infection or presence of chronic metabolic or neurological disorders (Belkaid Y and Hand T, 2014).
- **Autophagy** refers to a process by which the cytoplasmic materials are degraded inside the lysosomes (Nguyen HTT et al., 2013).
- **Germ-free (GF) model** – An animal model raised in GF conditions that is devoid of complex microbiota.
- **Specific pathogen free (SPF) model -** control animal with a normal composition of GM and no specific pathogens.
- **Conventional or wild-type (WT) mice –** mice raised in a normal conventional environment
- **Humanized gnotobiotic mouse model** - GF mice that receive faecal microbiota transplantation (FMT) of human faeces (John Chulhoon Park and Sin-Hyeog Im, 2020).

The bidirectional communication of the GBA occurs via complex and multiple pathways (Dalile et al., 2019). Although the precise pathways involved in GBA remains to be fully determined, there are direct [enteric nervous system (ENS) and vagus nerve) and indirect [such

as neurotransmitters, short chain fatty acids (SCFAs), and cytokines] routes through which gut microbes communicate to central nervous system (CNS) and vice versa (Sender et al., 2016). Gut microbes directly influence CNS processes via the neuroendocrine system (cortisol secretion via hypothalamic-pituitary adrenal (HPA) axis) (Mudd et al., 2017); the sympathetic and parasympathetic nervous system (Collins et al., 2012; Collins and Bercik, 2009) and vagus nerve (Forsythe et al., 2014), by producing bacterial metabolites (Dinan and Cryan, 2015; O' Mahony et al., 2015; Sherwin et al., 2016) **(Fig. 1)**.

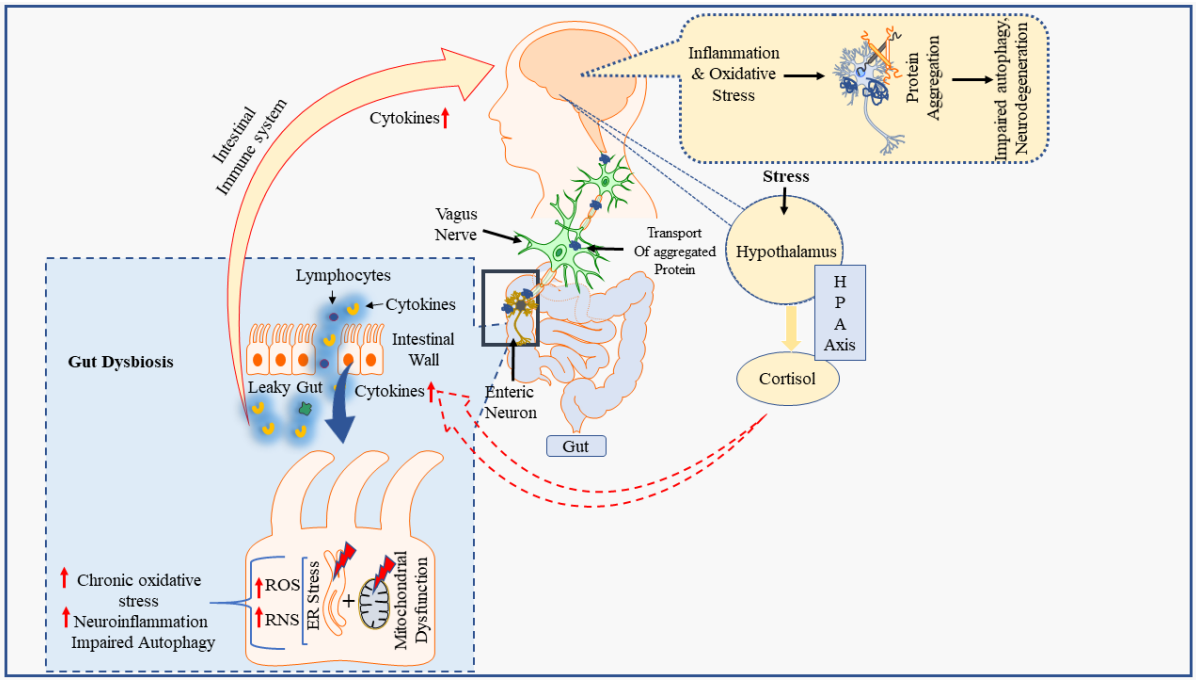


Fig. 1: Bidirectional communication between the gut microbiota and brain comprises direct [via the enteric nervous system (ENS) and vagus nerve) and indirect (by secreting neurotransmitters, short chain fatty acids (SCFAs), and cytokines] pathways of the gut-brain axis (GBA) which are modulated by the gut microbiota. These routes include the neural pathway (such as vagus nerve, ENS, neurotransmitters and metabolites such as SCFAs), immune pathways (including cytokine production), and neuroendocrine pathways [secretion of gut hormones by intestinal epithelial cells (IECs) and cortisol via the HPA axis]. Increased number of pathobionts with higher levels of toxic metabolites and cytokine production in the systemic circulation along with absence of beneficial metabolites dysregulates the GBA signalling, resulting in gut dysbiosis that affects the blood-brain-barrier (BBB) and immune system. Both the intestinal and nerve cells show defective autophagy with increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), dysfunctional mitochondria, and increased endoplasmic reticulum (ER) stress aggravates oxidative stress (OS), inflammation, and proteinopathies, which are relevant to neurodegenerative disorders (NDDs).

Gut microbes indirectly communicate with the CNS/ENS by producing several neuroactive metabolites such as SCFAs or branched-chain amino acids, lipopolysaccharide (LPS), bile acids, and catecholamines (Dalile et al., 2019; Fung et al., 2017)), synthesizing neurotransmitters with neuromodulatory properties including tryptophan precursors and metabolites, 5-hydroxytryptamine (5-HT or serotonin), gamma aminobutyric acid (GABA), glutamine, histamine, dopamine, and noradrenaline (Calvani et al., 2018; Fung et al., 2017; Sherwin et al., 2018), and gut hormones such as peptide YY, neuropeptide Y, ghrelin, leptin, cholecystokinin (CCK),and glucagon-like peptide-1 (Lyte, 2011; Sarkar et al., 2016). These important dietary and microbes-derived metabolites modulate the GBA to affect intestinal mucosal barrier function, hormone secretion from enteroendocrine cells (EECs), neurotransmitter release by gut epithelium and gut microbiota, as well as enteric glial signalling, neurogenesis, glial cell function, myelination, synaptic pruning, and BBB function (Heiss and Olofsson, 2019; Mukhtar et al., 2019), which are biologically relevant in the context of NDDs. Short chain fatty acids are one of the most important class of metabolites, performing a range of host processes such as energy utilization, host-microbe signalling, and regulation of colonic pH, with consequent effects on gut microbiota composition, gut motility, and epithelial cell proliferation (Musso et al., 2011). These SCFAs are also known to play a crucial role in the regulation of morphology and maturation of microglia (Erny et al., 2015).

The CNS also communicates via the autonomic nervous system [(ANS); both afferent and efferent autonomic pathways) and the ENS (Nair et al., 2018; Tysnes and Storstein, 2017) to the gut. Thus, the brain regulates gut motility and secretion of mucus and anti-microbial peptides as well as mucosal immunity and permeability (Browning and Travagli, 2014; Foster et al., 2017;).

1.1.1. Gut microbiota and HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis comprises the major part of the neuroendocrine system (mainly via the vagus nerve) in the GBA regulating body functions in response to stress stimuli (Smith SM and Vale WW, 2006). The HPA axis responds to stress signals by transferring hormones across the BBB through the circulatory system (Sudo, 2014). Studies have shown that gut microbiome programs the early activation of the HPA axis in response to psychological and physical stressors (Sudo N et al., 2004; Mudd AT et al., 2017).

During gut dysbiosis, cytokines ((IL-1β, IL-6 and TNF-α) and small bioactive molecules released excessively enter the brain via the BBB and activate the HPA axis (Banks, 2005). The HPA axis can be also activated by the release of lipopolysaccharide (LPS) (Vakharia and Hinson, 2005) and peptidoglycan (component of the most bacterial cell wall) (Arentsen et al., 2017). Moreover, early-life stress-mediated hyperactivation of the HPA axis results in altered microbial composition and increase GI permeability (Kelly JR et al., 2015). Increased exposure to corticosteroids causes changes in glucocorticoid receptor expression in the developing brain (van Bodegom M et al., 2017) and increased activity of the innate immune system (Danese A and Baldwin JR, 2017). Germ-free (GF) mice were found to present with significantly higher HPA response to stress when compared to the wild type mice (Clarke et al., 2014). Further, recolonization with complex microbiota at an early stage (up to 9 weeks old), partially reverses the elevated HPA response to stress (Sudo N et al., 2004). Likewise, GF mice displayed an elevated response to restraint stress (Sudo N et al., 2004) or emotional stress (maternal separation) (Murakami, T et al., 2017) vs. wild type mice. Notably, the increased brain stress-response in GF mice correlated with higher levels of brain corticotropin-releasing hormone, serum corticosterone, lower expression of glucocorticoid receptors, and reduced levels of brain-derived neurotrophic factor (BDNF), compared to SPF mice (Crumeyrolle-Arias et al., 2014; Luo et al., 2018). Indeed, it has been reported that the ratio of mineralocorticoid receptor to glucocorticoid receptor was reduced in the hypothalamus of

stressed GF mice, compared to GF control mice (Huo R et al., 2017). Studies in GF mice (Murakami, T et al., 2017), dogs (Rubio CA et al., 1992) and rats (Murakami, T et al., 2017) have shown that stress stimuli also altered mucus secretion, gut integrity, intestinal motility and microbial composition. In another study (Jang HM et al., 2018), mice subjected to immobilization stress showed anxiety-like behavior, elevated corticosterone levels in the blood, increased NF-κB activation via the HPA axis and microglia/monocyte populations in the hippocampus, and reduced BDNF expression in the hippocampus. These data indicates that gut microbiome alters HPA axis function which may lead to neurological complications.

1.2. Gut microbiota-derived neuroactive metabolites

Gut microbes produce a variety of neurotransmitters, neuromodulators and neurohormones, which are used as "words" of a common language, enabling a synergic bidirectional communication between the enteric and central nervous systems either directly via the vagus nerve or indirectly via the immune-mediated inflammatory pathways like microbial-driven systemic inflammation or stressors (Arpaia N et al., 2013; Smith PM et al., 2013).

Gut microorganisms induce the secretion of neuromodulatory metabolites, such as short chain fatty acids (SCFAs), as well as induce the production of host-derived vitamins (B12), neurotransmitters (eg, serotonin, catecholamines, glutamate, γ-aminobutyric acid (GABA)) (Foster JA et al., 2013; Mazzoli R et al., 2016), and hormones (peptide YY, neuropeptide Y, cholecystokinin, glucagon-like peptide-1 and 2, and substance P) that may impact host health (Zhao L et al., 2018; Jenkins TA et al., 2016; Erny D et al., 2015).

1.2.1. Short chain fatty acids (SCFAs)

The SCFAs are important metabolites produced in the colon by anaerobic fermentation of indigestible polysaccharides such as dietary fibres and resistant starch (Louis P and Flint HJ,

2009). These SCFAs are mostly comprised of acetate (40–60%), propionate (20–25%) and butyrate (15–20%) (Tan J et al., 2014). Specifically, Bacteroidetes phylum produces acetate and propionate, while Firmicutes phylum produce large amounts of butyrate (Macfarlane S and Macfarlane GT, 2003). Microbial-derived SCFAs are absorbed by colonocytes, mainly via H^+-dependent or Na^{2+}dependent monocarboxylate transporters (Viajy and Morris, 2014). These SCFAs bind to G protein-coupled receptors (GPCRs) in the GI mucosa as well as the immune and nervous systems; the effects of activation of GPCRs differ greatly depending on the cell on which they are expressed (Bolognini D et al., 2016). SCFAs can trigger the sympathetic nervous system, induce the release of serotonin, and modulate brain memory and learning processes (Erny D et al., 2015).

In the colon, SCFAs maintain the integrity of intestinal barrier, mucosal immunity, and protect the gut against inflammation (Lewis K et al., 2010; O'Keefe SJD, 2016). Furthermore, SCFAs have a direct influence on the permeability of the blood-gut barrier (Manfredsson et al., 2018). The SCFAs are translocated from colonic mucosa to systemic circulation (Schönfeld and Wojtczak, 2016). In the systemic circulation, SCFAs cause activation of brown adipose tissue (Li Z et al., 2018), regulation of liver mitochondrial function (Mollica MP et al., 2017), and whole-body energy homeostasis (De Vadder F et al., 2014). They also exert several effects on host metabolism and the immune system (Silva et al., 2020). In the colon, SCFAs (mainly butyrate) regulates the systemic inflammation by inducing the differentiation of T-regulatory cells (Treg) and the secretion of interleukins (Haghikia et al., 2015; Smith PM et al., 2013).

In the CNS, SCFAs regulate early neural system development, as they promote the growth of human neural progenitor cells and induce more cells to undergo mitosis (Yang LL et al., 2019). SCFAs play a central role in brain development and the preservation of CNS homeostasis (Braniste V et al., 2015; Hoyles L et al., 2018). SCFAs upregulate the expression of tight junction proteins such as claudin and occludin in the BBB, and they can pass through the BBB

via monocarboxylate transporters on the endothelial cells. SCFAs have been shown to extensively influence CNS function by modulating the levels of neurotrophic factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and neurotransmitters, and neuroinflammation by affecting glial cell morphology and function, mitochondrial function, immune activation, lipid metabolism, and gene expression (Varela RB et al., 2015; Wilton DK et al., 2019). Moreover, SCFAs can induce intracellular acidification which can modify calcium signalling, the release of neurotransmitters, and inhibition of gap junctions, potentially modifying neuronal communication and behaviour (Mirzaei et al., 2021). Further, SCFAs show several effects on neural functions, such as enhancing sleep (Szentirmai É et al., 2019) and contributing to circadian rhythm and appetite control (Torres-Fuentes C et al., 2019). Recent studies have also shown that SCFAs regulate the maintenance, maturation and function of microglia in a healthy functional state (Erny et al., 2015). The roles of SCFAs in various CNS- related diseases have recently been extensively reviewed by Silva et al., 2020 and Mirzaei et al., 2021.

Another important mechanism by which SCFAs regulate systemic functions is through inhibition of histone deacetylase (HDAC) activity, thus promoting the acetylation of lysine residues present in nucleosomal histones throughout various cell populations in the gut and associated immune tissue, as well as PNS and CNS (Silva et al., 2020). By virtue of their HDAC inhibitory activity, the SCFAs can promote the accumulation of transcriptionally permissive acetyl modifications at gene enhancers and promoters, which results in epigenetically regulated gene expression (Reddy DS et al., 2018; Watt et al., 2020). Thus, SCFA can manipulate the acetylation and methylation state and can regulate the gene expression and metabolic processes (Kasubuchi M et al., 2015).

Both in vivo and in vitro studies have shown that butyrate treatment alters the morphological and functional profile of microglia towards a homeostatic state and reduces LPS-induced pro-

inflammatory modifications and depression-like behaviour in mouse model (Wang P et al., 2018; Yamawaki et al., 2017). Similarly, in an in vitro model, exposure of microglia and astrocyte primary cultures with acetate has been shown to reduce inflammatory cytokines (IL-1β, IL-6, and TNF-α expression) by modulating p38 MAPK, JNK, and NF-κB signalling pathways (Soliman ML et al., 2012 and 2013). Likewise, propionate treatment on cerebrovascular endothelial cells has been shown to reduce the permeabilizing effects of BBB when exposed to LPS (Hoyles L et al., 2018). In summary, SCFAs interact with GBA and may directly or indirectly influence emotions, cognition, memory and behaviour as well as brain disorder pathophysiology.

1.2.2. Neurotransmitters

Contrary to conventional neurochemical construct, the proportion of total body levels of various neurotransmitters is significantly higher in the gut than the brain. SCFAs modulate the levels of excitatory and inhibitory neurotransmitters such as acetylcholine, dopamine, norepinephrine, epinephrine, GABA, serotonin, glutamate, and histamine, which are essential for proper brain functioning (Wang S et al., 2018), mainly by regulating amino acid catabolism. Several bacterial strains can modify the levels of neurotransmitter precursors available in the gut and even independently synthesize (or modulate the synthesis of) a number of neurotransmitters like GABA, serotonin, dopamine and noradrenaline.

It is noteworthy that enterochromaffin cells (special enteroendocrine cells in the gut) synthesize more than 90% of serotonin in the body (Bellono NW et al., 2017). From the gut, these microbial-derived neurotransmitters enter the circulatory system and influence neurological function either directly by entering the brain via the BBB (Sherwin E et al., 2018, Calvani R et al., 2018; Fung TC et al., 2017) or indirectly affect central neurocircuits by interfering with vagal nerve activity (Alam R et al., 2017). Growing evidence suggests that specific strains

secrete selective neurotransmitters. For example, *Bacillus* species mostly secrete acetylcholine, dopamine and noradrenaline, while dopamine, serotonin and noradrenaline are mainly secreted by *Escherichia* species (Johnson and Foster, 2018). The SCFA acetate has previously been shown to alter the levels of the neurotransmitters such as glutamate, glutamine and GABA in the hypothalamus and increase anorexigenic neuropeptide expression (Frost G et al., 2014).

GABA is a major inhibitory neurotransmitter in the CNS whose dysfunction is associated with depression, anxiety, autism, and schizophrenia (Barrett E et al., 2012). Among all human-derived strains cultured, *Lactobacillus brevis* and *Bifidobacterium dentium* are the most efficient GABA-producing species (Barrett et al., 2012). These microbes metabolize glutamate by regulating the expression of glutamate decarboxylase in human colon (Hyland NP and Cryan JF 2010; Bravo JA et al., 2011). Interestingly, gut-derived GABA can cross the BBB and enter the CNS, thus highlighting the correlation between gut dysbiosis and mental disorders (Takanaga et al. 2001). Studies show that gut microbes regulate GABA signalling to CNS mainly through the vagus nerve, as chronic administration of *Lactobacillus rhamnosus* increased the central expression of GABA receptors in the hippocampus and reduced anxiety- and depression-related behaviours only in mice with intact vagus nerve; however, these anxiolytic effects are lost after vagotomy (Bravo JA et al., 2011; Janik R et al., 2016). Growing evidence suggests that some bacterial strains of the human gut microbiota can monitor and probably respond to intestinal GABA or glutamate (Mazzoli R and Pessione E, 2016). GF mice show lower levels of GABA in the serum together with altered levels of specific precursors and metabolites in the intestine (Matsumoto et al., 2012; Velagapudi et al., 2010).

It is important to note that GABA is produced in both eukaryotes and prokaryotes via glutamate decarboxylation. Hence, GABA-producing microbes in the gut may significantly affect luminal glutamate/GABA ratio and, therefore, gut signalling. Perturbations in glutamate, glutamine and

GABA circuits in the CNS are often found in generalized anxiety disorders, major depressive disorder (MDD), manic depressive disorder (or bipolar disorder) and schizophrenia (Femenía et al., 2012; Soeiro-de-Souza et al., 2015).

It is worth noting that gut microbial dysbiosis in patients with hepatic encephalopathy (HE) is characterized by reduced gut microbial diversity. Pathogenesis of HE includes ammonia intoxication, impaired bile acid circulation, elevated GABA levels, and neuroinflammation, which leads to cognitive and motor disorders in patients. BBB damage in HE patients has been linked with the swelling of astrocytes, endothelial cell damage, and the opening of tight junctions. Likewise, *Enterobacteriaceae* and *Autochthonous taxa* were found to be positively and negatively correlated with astrocyte swelling, respectively (Ahluwalia V et al., 2016). SCFAs levels are found to be significantly reduced in cirrhosis patients with HE (Jin M et al., 2019). In brain of HE patients, excessive glutamate binds to ammonia and produces glutamine accumulation leading to brain oedema, and learning and memory impairment (Cabrera-Pastor A et al., 2019). Similarly, colonic mucosal autochthonous genera (*Lachnospiraceae Roseburia*, *Lachnospiraceae Dorea*, and *Ruminococcaceae Fecalibacterium*) were associated with good cognitive performance, while others (*Burkholderiaceae*, *Veillonellaceae Megaspheara*, *Rikenellaceae*, *Alistipes*, *Streptococcaceae*, *Alcaligenceae*, *Sutterella*, *Porphyromonadaceae*, and *Parabacteroides*) were linked with cognitive impairment in HE patients (Teltschik Z et al., 2012).

Glutamate - Glutamate is the major excitatory neurotransmitter that regulates CNS and PNS via NMDA and AMPA receptors (Martinez-Lozada and Ortega, 2015). Several bacterial strains are able to produce glutamate. In industries, Coryneform bacteria, such as *Corynebacterium glutamicum*, *Brevibacterium lactofermentum* and *Brevibacterium flavum*, are widely used for fermentative production of glutamate (Sano, 2009). Further, strains of lactic acid bacteria such as *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Lactococcus*

lactis are capable of synthesizing glutamate (Tanous et al., 2005). Approximately 15% of lactic acid-producing bacterial strains which are found in Asian fermented foods can produce glutamate (Zareian et al., 2012).

Serotonin and Catecholamines – Microbial-derived SCFAs stimulate the secretion of serotonin (5-HT) by enterochromaffin cells (Reigstad CS et al., 2014; Yano et al., 2015) in the gut by regulating the expression levels of tryptophan 5-hydroxylase 1 (the enzyme involved in synthesis of serotonin), and tyrosine hydroxylase (a rate-limiting enzyme) involved in the biosynthesis of dopamine, noradrenaline and adrenaline (Mittal R et al., 2017). In addition to the inability to cross the blood-brain barrier (BBB), the microbiome controls the 5-HT turnover in the brain by altering the 5-HT precursor levels (O'Mahony et al., 2015; Sharon et al., 2014). Similarly, GF mice also display reduced levels of brain-derived neurotropic factor, 5-HT, and specific 5-HT receptors (5HT1A) in the amygdala and hippocampus (Clarke et al., 2013; Neufeld et al., 2011). The GM directly uses tryptophan (an essential amino acid that acts as a precursor for serotonin and kynurenine production), thus reducing its availability to the host (O'Mahony SM et al., 2015). Certain bacterial species metabolize tryptophan into indole, while other gut bacteria can synthesize tryptophan or even produce 5-HT from tryptophan (O'Mahony SM et al., 2015). Both the local stimulation in the brain and production of 5-HT in the gut have important effects on host physiology as it regulates GI motility (Berger et al., 2009). Therefore, SCFAs-mediated changes in neurotransmitters can produce an effect on brain neurochemistry (Clarke G et al., 2014; Yano JM et al., 2015).

1.2.3. Trimethylamine N-oxide (TMAO)

Gut microbes metabolize trimethylamine N-oxide (TMAO) to trimethylamine (TMA) obtained from dietary nutrients (like choline, phosphatidylcholine, lecithin and L-carnitine) by ingesting foods like marine fish, eggs, liver, legumes (such as soybeans and peas). TMA is absorbed by

passive diffusion across the cell membranes (Zeisel SH et al., 1989) and enters the liver by enterohepatic circulation, where TMA (malodorous metabolite) is oxygenated back to the odourless TMAO (non-odorous hepatic metabolite) by flavin-containing monooxygenase 3 (FMO3) (Ziegler DM, 1988) (Cruciani G et al., 2014; Zhu et al., 2017). The FMO3 gene belongs to the family of FMO genes, and encodes for a transmembrane protein localized to the endoplasmic reticulum of several tissues, particularly in the liver (Esposito T et al., 2014).

Differential production of SCFAs (resulted from mixed acid fermentation), together with lactate and α-ketoglutarate play a major role in the synthesis of neurotransmitters such as glutamate, GABA, serotonin and catecholamine, whose concentration could possibly interfere with betaine transport, leading to increased levels of TMA accumulation (Silva Y et al., 2020; Jenkins TA et al., 2016; Murphy MM et al., 2020). High levels of TMA lead to trimethylaminuria, a rare metabolic disorder caused by dysfunctional metabolism of dietary-derived TMA by FMO3. Trimethylaminuria is also known as fish odor syndrome due to the fishy smell in the urine, sweat and breath of *FMO3-deficient* patients (Jeffrey Messenger et al., 2013). The primary form of trimethylaminuria phenotype is mainly characterized by the genetic mutations in FMO3 gene (Phillips IR et al., 2020), while secondary trimethylaminuria is determined by other non-genetics factors such as gut microbiome dysbiosis (Schmidt AC and Leroux JC, 2020). Reports indicate that the *Clostridiales*, *Lachnospiraceae*, and *Ruminococcus* are directly correlat with the TMAO levels in the plasma. Cases of trimethylaminuria were reported after treatment with choline (8–20 g/day) in patients with Huntington's disease and Alzheimer's disease (Growdon JH et al., 1977; Etienne P et al., 1978). Neuropathological conditions associated with trimethylaminuria include oxidative stress and inflammation leading endothelial dysfunction and increased BBB permeability. Under chronic conditions, these changes lead to excessive excitotoxicity, responsible for neuronal degeneration (GU M et al., 2020).

2. Molecular pathological commonalities in neurodegenerative diseases

Neurodegenerative diseases manifest with distinct clinical features and affect specific regions of the brain. They share close molecular pathologies with “Proteinopathies”; diseases where proteins are abnormally self-associating and aggregating, due to conformational changes, which induce neurotoxic effects (Borre et al., 2014; Sender et al., 2016). In addition to the protein aggregates, NDDs also exhibit an accumulation of dysfunctional mitochondria, increased OS (Greco et al., 2019), and defective autophagy (Hara et al., 2006), which further aggravates chronic neuroinflammation caused by a dysregulated immune response due to gut dysbiosis and impaired GBA signalling (Donaldson et al., 2016; Quigley, 2017).

2.1. Proteinopathies

Proteinopathies are characterized by the deposition of misfolded disease-specific proteins inside and/or outside various CNS cells, either as small oligomeric (extracellularly) or large fibrillary aggregates (intracellularly) (Bayer, 2015; Golde and Miller, 2009) **(Fig. 2)**. In addition, the molecular mechanisms involved in conformational changes of misfolded proteins are found to be similar across all types of proteinopathies, which mostly include post-translational modifications of both size and 3D-shape, the loss of protein clearance (impaired autophagy) or the enhancement of protein production, leading to elongation, aggregation, and precipitation in specific brain regions, thereby imparting neurotoxicity (Sami et al., 2017; Soto and Pritzkow, 2018). The general pathophysiology of seeding and propagation of misfolded proteins in several NDDs are discussed below.

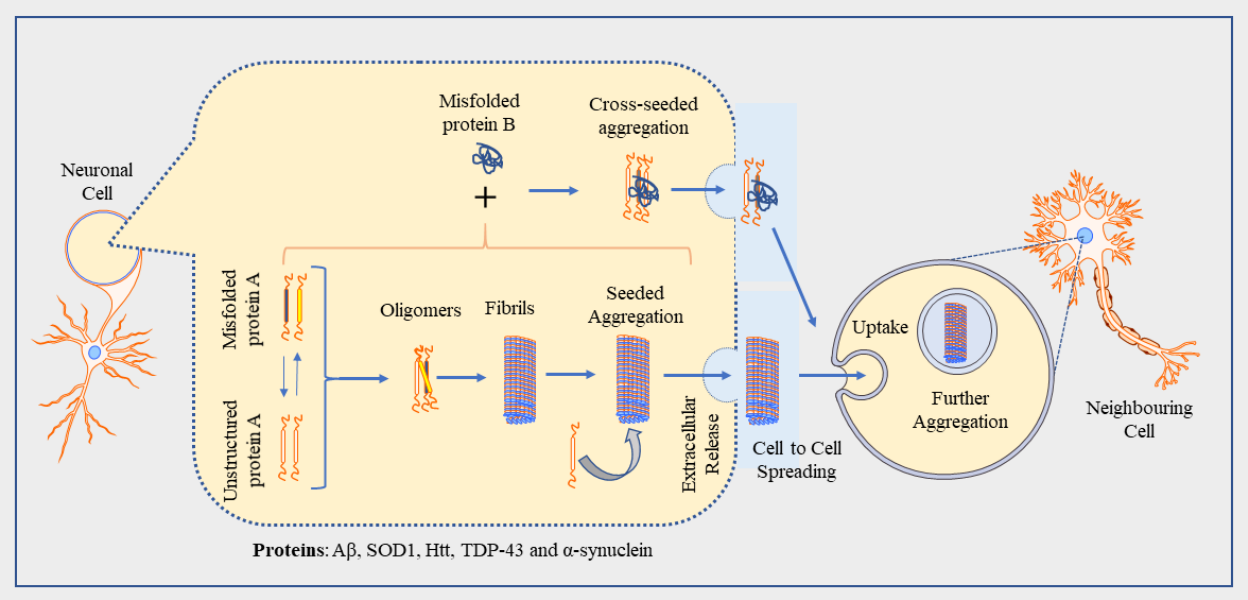


Fig. 2. Protein aggregations in neuron. In neurons, impaired autophagy and increased oxidative stress (OS), exposure to proinflammatory cytokines and toxic metabolites propagates the misfolding of unstructured proteins into oligomers, which converge into fibrils and form toxic aggregates. These aggregates facilitate seeding or nucleation and trigger the misfolding of other naïve proteins, resulting in proteinopathies. This pathogenic process causes neurotoxicity and cell death. Proteinopathies spread in a prion-like manner from cell to cell or cause death of neurons which causes the release of toxic aggregates. These aggregates are internalized by the neighbouring cells. Misfolded proteins induce cross-seeding by triggering conformational changes to other toxic structural forms.

2.2. Seed or nucleation

In most NDDs, genetic factors and natural aging are the primary triggers for the unstructured proteins to undergo structural modifications and form misfolded proteins, which self-transform their shape and propagate the fragments by autocatalytic amplification forming small oligomeric or large fibrillary aggregates in and around the CNS cells. CNS-associated proteinopathies spread in a prion-like fashion within the GBA (Jucker and Walker, 2011; Polymenidou and Cleveland, 2012) and are commonly referred as ‘Prionoids’. In prions disease, the highly infective misfolded prions transmit from cell-to-cell within the CNS (Ugalde et al., 2020). Similarly, the structural modification of the native α-helical protein to a toxic β-sheet amyloid structure triggers the misfolding of other native proteins to form β-sheet rich aggregates (Taylor-Walker et al., 2016; Ugalde et al., 2016) in a self-perpetuating process in AD and PD (Visanji et al., 2013). Similarly, mutant Huntingtin (mHTT) is detected in the

early stages of the HD and regulate the template for the misfolded proteins aggregation which seeds and propagates across the cells and in turn even serve as biomarker for the determination of disease progression (XX; XXX). Thus, the abnormal protein acts as a seed or template for protein misfolding, and this process is called "**Seeding or Nucleation"**. Once seeded, growth of misfolded proteins (e.g., prions, αSyn, Aβ or Htt) is significantly exponential leading to rapid formation of macromolecular structures that appear as intracellular inclusions or extracellular deposits. Neurodegenerative disease (NDD)-related proteinopathies are classified as "pure" when the protein aggregates are of single type, or as "mixed" when the deposits are composed of different misfolded protein classes (Scheperjans et al., 2015; Walker and Jucker, 2015).

2.3. Propagation

Proteins implicated in proteinopathies are largely localized to the nucleus, cytoplasm, or part of the scaffolding network of the cell, but evidence shows that these pathological proteins are secreted and are present at low levels in interstitial and cerebrospinal fluid (Polymenidou and Cleveland, 2012; Yamada et al., 2011). Furthermore, microbially-produced amyloids are released into the extracellular space, where they are internalized by adjacent enteric neurons and thus, new seeds of the αSyn form via permissive templating (Soto and Pritzkow, 2018). The spreading of the neurotoxic aggregates may occur from molecule-to-molecule inside a cell, cell-to-cell in a specific region and region-to-region in the CNS. Both in vitro and in vivo studies of NDDs show that tau, Aβ, SOD1, Htt, transactive response DNA binding protein with a molecular weight of 43 kDa (TDP-43) and αSyn, are secreted by neurons through non-classical exocytosis in the form of exosomes, microvesicles and tunnelling nanotubes into the extracellular milieu (Chia et al., 2017; Luk et al., 2012). These extracellular aggregates act as damage-associated molecular patterns (DAMPs) and "seeds", and are internalized by

neighbouring neurons or glial cells though endocytosis, leading to the misfolding of native proteins in the recipient cell into aggregates and/or fibrils to form new aggregates (Jucker and Walker, 2018; Prymaczok et al., 2016). Finally, extracellular aggregates secreted by the recipient cells set off a vicious cycle of further aggregate secretion, inflammation, and reseeding that propagates the pathology; **(Fig. 2)**.

2.4. Cross-seeding

Prions propagate via self-seeding in which a protein in a prion conformation causes another molecule of the same protein to adopt an amyloid conformation (Prusiner, 2013). However, here are several examples of infectious amyloids capable of cross-seeding each other (Furukawa et al., 2009; Lasagna-Reeves et al., 2010) and triggering various types of secondary proteinopathies to a varying extent via prionoid-like mechanisms (R et al., 2010). Bacterial amyloid and amyloids derived from other sources cross-seed the formation of additional neural protein aggregates or may be endocytosed by enteric nerves (S. G. Chen et al., 2016; Friedland, 2015). For instance, Curli proteins from different bacterial species are capable of cross-seeding amyloid formation both in vitro and in vivo (Zhou et al., 2012). Additionally, NDDs-associated amyloid proteins, such as αSyn or Aß, may have strain specificity in a manner analogous to the strains of prion disease (Hatami et al., 2014). Furthermore, several bacterial amyloids may trigger cross-seeding in a strain-specific manner, consequently resulting in multiple proteinopathies. Indeed, AD is not only characterized by Aβ and tau pathology, but also by αSyn and TDP-43 pathology in a subset of cases (Gidalevitz et al., 2006). However, additional investigations into pathological mechanisms are necessary to confirm these findings.

3. The role of gut dysbiosis on the pathophysiology of neurodegenerative diseases

The close interaction between intrinsic (age, genetic) and extrinsic (environmental) factors is suggested to initiate the pathological processes of NDDs (Jellinger, 2010), but recent evidence

618 also shows that gut dysbiosis disrupts brain and gut homeostasis that worsens pathogenesis
619 and/or the progression of NDDs (Dinan and Cryan, 2017; Tyler Patterson and Grandhi, 2020).
620 Specifically, an increase in pathogenic bacteria (pathobionts) along with a decrease in
621 beneficial bacteria (symbionts) defines gut dysbiosis in NDDs (Dinan and Cryan, 2017;
622 O'Toole and Jeffery, 2015). In this sense, gut dysbiosis is directly linked to the development
623 of diseases/disorders associated with functional metabolic perturbations. For instance, a gut
624 microbial-mediated metabolite named TMAO is involved in the increased risk of AD (Xu and
625 Wang, 2016).
626
627 Similarly, brain samples of AD, PD and ALS patients showed increased abundance of
628 cyanobacteria in the gut, which secretes higher levels of β-N-methylamino-L-alanine (BMAA),
629 an excitotoxin that binds to metabotropic glutamate receptor 5 and depletes major antioxidant
630 glutathione. This results in excessive production of reactive oxygen species (ROS) and reactive
631 nitrogen species (RNS) in the brain, suggesting the direct link between gut dysbiosis and OS
632 in NDDs. The non-proteinogenic amino acid β-N-methylamino-L-alanine is also found to
633 promote misfolding and aggregation, distinctly found in NDDs (Brenner, 2013).
634 The main pathological processes in the initiation of NDDs include defective gut epithelial
635 barrier due to changes in tight junctions; altered secretion of mucus and neuroactive-microbial
636 molecules such as SCFAs (Luan et al., 2019); and increased secretion of immunoglobulin A
637 (König et al., 2016; Wells et al., 2017), which causes immune-mediated inflammation (Amor
638 and Woodroofe, 2014) in the colon and brain. Chronic neuroinflammation promotes the
639 aggregation and accumulation of misfolded proteins in the CNS cells. Moreover, increased
640 permeability of the BBB and the blood-gut barrier (Manfredsson et al., 2018) along with low
641 levels of 5-HT due to compromised microbial metabolism of tryptophan (Agus et al., 2018;
642 Yano et al., 2015), alters brain homeostasis. Stress in the CNS activates cortisol secretion
643 (Cryan and Dinan, 2012), which in turn promotes immune cell recruitment, cytokine secretion,

and increased epithelial barrier permeability, leading to translocation of overgrowth of pathobionts and release of neurotoxic microbial fragments, such as LPS. The continuous infiltration of blood-borne immune cells, other inflammatory cells, and gut metabolites into the CNS through the compromised BBB (Borre et al., 2014; Perez-Pardo et al., 2019) characterizes the progression of NDDs (Sevenich, 2018). Chronic neuroinflammation (Sevenich, 2018; Solleiro-Villavicencio and Rivas-Arancibia, 2018) due to increased levels of proinflammatory molecules enhances the neuronal cell permeability, leading to alteration and/or destruction of synapses and other cellular processes. These changes result in neuronal death and the release of misfolded neurotoxic aggregates, which reinforce the pathological positive feedback loop (Dalile et al., 2019). Gut dysbiosis-mediated neuroinflammatory activity associates with a state of chronic OS (Filomeni et al., 2015), and represents an important hallmark of NDDs (Mittal et al., 2014). Altogether, emerging evidence clearly shows that gut dysbiosis-mediated dysfunction in GBA signalling is linked to the development of neurodegeneration (Borre et al., 2014; Luan et al., 2019), which ultimately results in abnormal behaviour, cognitive impairment, stress and visceral pain (Cryan and Dinan, 2012).

3.1. Gut dysbiosis and defective autophagy

Autophagy is a regulated degradation process which eliminates unwanted proteins and permeabilized mitochondria, thus supporting cellular and tissue homeostasis (Green et al., 2011). Several studies have shown that autophagy has a great significance in maintaining the intestinal epithelial barrier integrity and homeostasis, anti-microbial defence (Mizushima, 2018) and regulating intestinal innate and adaptive immunity (Kabat et al., 2016). Emerging evidence shows that gut microbiota-derived metabolites regulate intestinal inflammation via the autophagy pathway. In addition, autophagy in turn degrades invading pathogens (e.g., *Salmonella enterica and Escherichia coli*), modulates the pathogen triggered release of pro-

669 inflammatory cytokines, and involved in antigen presentation and lymphocyte development
670 (Boya et al., 2013; Elshaer and Begun, 2017).
671 A growing body of literature suggests that the gut microbiota and autophagy also exhibit a
672 bidirectional relationship. Defective autophagy induces gut dysbiosis and gut dysbiosis can
673 also cause defective autophagy in IECs including paneth and goblet cells, EECs, macrophages,
674 dendritic cells (DCs), T and B cells, natural killer cells, nerve cells of ENS, ANS and CNS,
675 and glial cells, mainly by disturbing mitochondrial dynamics (Saint-Georges-Chaumet and
676 Edeas, 2016; Yudong Wang et al., 2019). Mounting evidence states that the dysregulated
677 autophagy leads to disrupted intestinal epithelial barrier function by altering the expression
678 of tight junction protein CLDN2 (claudin 2) levels in intestinal mucosa (Nighot et al., 2015; C.
679 Zhang et al., 2017), and increased bacterial translocation and dissemination, particularly IgA-
680 coated bacterial levels (Tsuboi et al., 2015; Yang et al., 2018), which results in gut dysbiosis;
681 a reduction in the secretion of anti-microbial peptides (such as lysozyme, α-defensin and
682 phospholipase A2) from paneth cells and mucins from goblet cells; impaired epithelium
683 regeneration in intestinal stem cells; defective intracellular bacterial clearance (Chauhan et al.,
684 2015; Lopes et al., 2018) , and exuberated immune responses to pathogenic bacteria (Kabat et
685 al., 2016; Xu et al., 2014).
686 The influence of autophagy deficiency on gut microbiota composition has been studied using
687 gut-specific autophagy-deficient mouse models (intestinal epithelium-specific autophagy-
688 related 5 (Atg5) knockout C57BL/6J or Atg5-deficient mice). Atg5-deficient mice demonstrate
689 a dramatic alteration and decreased diversity in their gut microbiota compared with that of
690 wild-type (WT) mice (Yang et al., 2018). Analysis at the genus level showed that 23, 25, 33,
691 35, and 23 genera were notably altered in the duodenum, jejunum-ileum, cecum, colon, and
692 faeces of Atg5-deficient mice, compared with the respective anatomical sites in control mice,
693 whilst analysis at the species level showed that 7, 10, 12, 14, and 13 species were significantly

694 different in Atg5-deficient mice from the controls, respectively. Interestingly, pro-
695 inflammatory bacteria (e.g., *Candidatus Arthromitus*) and pathobionts (members of the
696 *Pasteurellaceae* family) were enriched, whereas anti-inflammatory bacteria (e.g., *Akkermansia*
697 *muciniphila* and members of the *Lachnospiraceae* family) were reduced in Atg5-deficient
698 mice, confirming the presence of gut dysbiosis.
699 Similar to previous reports (Lévy et al., 2015), paneth cells of Atg5-deficient mice showed
700 morphological and functional abnormalities. Remarkably, decreased expression of defensins
701 and reduced levels of cytoplasmic lysozymes in these dysfunctional paneth cells were
702 associated with an altered gut microbiota composition (Salzman et al., 2010). These pathogenic
703 abnormalities increased the vulnerability of the host intestinal cells to pathogenic infections by
704 enhancing activation of the inflammatory pathways in the small intestinal segments (duodenum
705 and jejunum-ileum) of Atg5-deficient mice (Yang et al., 2018). Increased expression of MUC2
706 in goblet cells of Atg5-deficient mice was associated with the induction of high levels of ROS
707 (Yang et al., 2018). Among 349 differentially expressed genes detected by transcriptome
708 sequencing, 222 genes were upregulated and 127 genes were downregulated in Atg5-deficient
709 mice, while 40 immune-associated genes were found be highly expressed, including two key
710 IBD-related transcription factors, RORC and TBX21. Specifically, autophagy deficiency in the
711 IECs may induce an imbalance in the ratio of TH17/regulatory T (Treg) cells, which leads to
712 the development of autoimmune and inflammatory diseases (Noack and Miossec, 2014).
713 Gut dysbiosis-induced defective autophagy leads to excessive production of ROS, which
714 dysregulates mitochondria functions, stimulates ER stress and apoptosis in goblet cells, and
715 damages the cellular macromolecules such as DNA, lipids and proteins (Yudong Wang et al.,
716 2019). Subsequently, gut dysbiosis amplifies the OS scenario (Stilling and Cryan, 2016)
717 resulting in compromised intestinal mucus barrier function (Tawiah et al., 2018) and
718 exacerbates immune responses and neuroinflammation. In addition to the absence of

antioxidant signalling pathway (Filomeni et al., 2015), dysfunctional autophagy contributes to the pathogenesis of various NDDs such as AD and PD (Bonfili et al., 2017; Keshavarzian et al., 2015; Scheperjans et al., 2015).

Furthermore, dysregulated autophagy alters ER homeostasis triggering the accumulation of misfolded proteins intracellularly, leading to activation of unfolded protein response, autophagic response or apoptosis (Senft and Ronai, 2015) and extracellularly, leading to abnormal interaction of neurons with astrocytes and microglia, autoimmunity, impaired phagocytic clearance, and transport through the defective BBB (Chiti and Dobson, 2017; Sami et al., 2017, 2017). Genetic ablation of core autophagy genes (e.g., ATG genes) or genetic mutations of autophagy genes, causes significant deterioration of neuronal health in Drosophila flies and mice (Juhász et al., 2007; Komatsu et al., 2006). Specifically, autophagy-deficient neurons show excessive accumulation of ubiquitin/p62-positive protein inclusions and damaged mitochondria with altered ER stress response, leading to neuronal death and cognitive impairment (Kim et al., n.d.; Liang et al., 2010). These results indicate that autophagy plays an important role in neuronal homeostasis and neurodegenerative pathologies (Komatsu et al., 2006; Nixon, 2013). Indeed, both AD and PD are prominent NDDs with phenotypes indicative of defective autophagy. In vitro and in vivo AD models as well as the degenerating brain tissue samples of AD patients reveal defective autophagic flux with prominent accumulation of non-degraded autophagic vesicles (Nixon et al., 2005). Mutations in presenilin 1 (PS1) and the amyloid precursor protein (APP), found in familial AD, are known to trigger autophagic-lysosomal pathologies in both mouse (Wilson et al., 2004, p.; Yang et al., 2011) and cell culture models. Additionally, the expressions of Aβ, the cleavage product of APP, also induce the accumulation of large autophagic vesicles in the Drosophila brain (Ling et al., 2009). Analysis of familial PD reveal several causative autophagy-related genes called PARK genes (Lesage and Brice, 2009), including *PARK1* and *PARK4* (SNCA), *PARK2* (Parkin), *PARK5* (UCHL1*),*

PARK6 (PINK1), *PARK7* (DJ-1), *PARK8* (LRRK2) and *PARK9* (ATP13A2), involved in the autophagic elimination of ubiquitinated proteins or damaged mitochondria. The presence of these altered genes is further confirmed by the presence of protein aggregates and damaged mitochondria in the diseased tissues from PD, suggesting deregulated autophagy related with the progression of PD pathologies (Dehay et al., 2013; Lynch-Day et al., 2012).

Altogether, these results indicate that gut dysbiosis induced by autophagy deficiency may program a persistent immune response and enhance basal intestinal inflammation by exposing the host intestinal cells to excessive immune activation. Furthermore, the imbalance in the immune cells may provide the toxic inflammatory milieu, which promotes neuroinflammation and spread of misfolded proteins or toxic amyloids from the gut to the brain, which may be through the neural routes via exosomes, vesicles or nanotubes. Genetic changes in autophagy-related genes in the IECs, EECs, nerve and glial cells may further alter gut motility, permeability and mucus secretion, worsening intestinal inflammation via the signals from the brain to the gut. Hence, we speculate that the modulation of the gut microbiota using potential therapeutics may break the loop of excess immune activation and inflammation, restore the autophagy process, balance the ratio of the immune cells, and reduce the OS, inflammation, and spread of toxic misfolded protein aggregates, thus, halting the progression of NDDs.

3.2. Gut dysbiosis, impaired immune response, and neurodegeneration

Dysregulated immune activation due to gut dysbiosis (López-Valdés and Martínez-Coria, 2016) leads to gut barrier dysfunction and chronic inflammation which triggers the neurodegenerative machinery at various levels (Schwartz and Baruch, 2014; Schwartz and Deczkowska, 2016). The key inflammatory immune changes observed in gut dysbiosis include functional modulation of the DCs and glial cells in the CNS as well as host immune cells including effector T and B cells in the intestine, peripheral blood and PNS (Caputi and Giron,

2018). Further, the gut microbiota and their metabolites interact with different cellular components of the CNS via the activation of immune signalling pathways including the inflammasome, type 1 interferon, MyD88-dependent and NF-κB (Gagliani et al., 2014; Lu et al., 2018; Truax et al., 2018). Thus, chronic neuroinflammation due to excessive accumulation of lymphocytes, cytokines and chemokines (König et al., 2016; Wells et al., 2017) results in aggregation and accumulation of misfolded proteins in and around the neurons (Chitnis and Weiner, 2017; Schwartz and Baruch, 2014).

In terms of innate immunity, misfolded protein aggregates and amyloid deposits resemble PAMPs and thymus-independent type 2 (TI-2) antigens (Golde and Miller, 2009). PAMPs are the highly conserved microbial structures consisting of proteins, nucleotides, LPS, lipoteichoic acid (LTA), CpG, or dsRNAs, and are recognized as the pathogenic targets by PRRs from the host innate immune system (Medzhitov and Janeway, 2000). Gut microbes and their metabolites constantly interact with PRRs expressed in host immune IECs, EECs, and immune cells in peripheral blood as well as neurons and glial cells (microglia and astrocytes) of the CNS and PNS (Caputi and Giron, 2018; McKernan et al., 2011). TI-2 antigens are similar polymeric molecules that directly stimulate IgM secretion by B-cells. A plethora of experimental data has shown that amyloid-like deposits or protein aggregates can act like PAMPs leading to chronic innate immune activation by binding to a whole range of PRRs, including toll-like receptors (TLRs), formyl peptide receptors, the receptor for advanced glycation end products, scavenger receptors, complement and pentraxins (Golde and Miller, 2009; Rungratanawanich et al., 2021). In a chronic state of OS, increased levels of reactive oxygen and nitrogen species stimulates the secretion of proinflammatory molecules (cytokines and chemokines), neoepitopes and DAMPs, which in turn stimulates the microglia and astrocytes (Rothhammer et al., 2018; Sevenich, 2018; Solleiro-Villavicencio and Rivas-Arancibia, 2018). Moreover, due to the altered innate immune response, microglia with

794 immature phenotype and altered genetic profile (Erny et al., 2015) fail to remove the misfolded
795 protein deposits (due to impaired autophagy), leading to a vicious cycle characterized by pro-
796 inflammatory cytokine production linked to a toxic cascade and neuronal death (Schwartz and
797 Baruch, 2014).
798 Adaptive immunity also plays a crucial role in anti-microbial defence and the maintenance of
799 gut microbiota-host-metabolic homeostasis to prevent an exuberated immune response to
800 harmless antigens. Gut dysbiosis impacts NDDs through direct production of the metabolites
801 with neuroactive properties such as SCFA and neurotransmitters (Jayaraj et al., 2017; Solleiro-
802 Villavicencio and Rivas-Arancibia, 2018) and/or stimulation of proinflammatory molecules
803 including cytokines, chemokines, and gut peptides by the secretory epithelial cells (Wekerle,
804 2018). Under pathological conditions, these metabolites can cross the defective BBB and
805 trigger and/or amplify inflammatory brain processes by recruiting peripheral myeloid cells
806 (Quigley, 2017; Zhang and Davies, 2016), which in turn intensifies the activation of microglia
807 and astrocytes, therefore generating a vicious cycle (González et al., 2014; González and
808 Pacheco, 2014). Gut dysbiosis is also linked to reports of high frequencies of reactive T
809 lymphocytes in the bloodstream and CNS (Borre et al., 2014; Donaldson et al., 2016; Quigley,
810 2017; Sender et al., 2016), which impairs the transition and proliferation of T-cells in the
811 specific brain regions (Schwartz and Deczkowska, 2016). These events lead to decreased
812 numbers of $CD4^+$ and $CD8^+$ T subsets (Amor et al., 2010), impaired memory $CD8^+$ T cell
813 development, decreased Treg cell survival and increased Th2 and Th17 responses both in the
814 periphery and in the CNS. These changes trigger further recruitment of DCs, group 3 innate
815 lymphoid cells and granulocytes into the CNS (Honda and Littman, 2016). Dysbiotic signals
816 induce IL-23 overexpression in Th17 cells, and decrease the protective immunosuppression
817 signals delivered through GATA3, Foxp3, and IL-33 expression in Treg cells (Atarashi et al.,
818 2011; Pm et al., 2013), leading to chronic neuroinflammation associated with autoimmune

diseases and NDDs (Berer et al., 2011; Coccia et al., 2012; Horai et al., 2015). In addition, gut dysbiosis activates the secondary antibody response by B cells, which influences class switching of IgA in B cells (Zhao and Elson, 2018). Thus, the microbiome and its metabolites shape the host-immune system and vice-versa, while gut dysbiosis affects the host immune system mainly by stimulating inflammasome signalling.

It is thought that the adaptive immune system (such as T- and B-lymphocytes) plays an early causative role in autoimmune disorders of the CNS, such as ALS and MS. However, in AD and PD, activation of innate immune reactions which are normally protective, perpetuates proinflammatory triggers (Jayaraj et al., 2017; Solleiro-Villavicencio and Rivas-Arancibia, 2018). Together, with aberrant activity of microglia and astrocytes, these changes crucially contribute to neuronal loss and dysfunction that culminates in neurodegeneration (Jayaraj et al., 2017; Solleiro-Villavicencio and Rivas-Arancibia, 2018). Treg cells have also been proposed as crucial players in NDDs such as AD, PD, and ALS (Baruch et al., 2015; Ciccocioppo et al., 2019; Dansokho et al., 2016; Pieragostino et al., 2019). However, recent studies in CNS-related diseases propose that gut dysbiosis can be the main triggering factor for immune-mediated chronic inflammation in which misfolded proteins of NDD spread from the PNS to the CNS via the GBA network. These cascade events lead to altered immune activation (Andreasson et al., 2016; Nataf, 2017) and disrupted protein clearance (Deleidi and Maetzler, 2012), providing a neurotoxic inflammatory milieu that aggravates the spread of aggregates in different brain regions, and results in a vicious cycle of the immune driven-inflammation and neuronal death.

Several studies shed light that combines neurodegeneration with gut dysbiosis-mediated GBA dysregulation (Golde and Miller, 2009; Schwartz and Baruch, 2014). In most NDDs, gut dysbiosis induce defective autophagy in IECs, EECs, macrophages, DCs, T cells, B cells, nerve cells and glial cells leads to increased OS, defective protein clearance and protein misfolding,

forming small oligomeric or large fibrillary aggregates. These misfolded aggregates trigger PRRs inducing inflammation in the gut and CNS. Additionally, the specific increase in gut pathobionts such as *Escherichia coli, Klebsiella pneumoniae, and Mycobacterium tuberculosis* produce more amyloid proteins, which act as potential seeds in the formation of Aβ misfolding in AD models (Friedland and Chapman, 2017). Gut dysbiosis-mediated altered SCFA profiles, decreased mucin production, and increased bacterial/antigen translocation lead to systemic inflammation as well as activation of microglia or enteric glia are found to contribute to αSyn misfolding in PD models (Minato et al., 2017; Mulak and Bonaz, 2015).

Overall, an imbalance of T-helper, Treg cells and DCs in the intestine as well as dysfunctional microglia and Treg cells in the brain parenchyma, initiates the toxic inflammatory cascade and neuronal death (Baruch et al., 2015; Ciccocioppo et al., 2019; Schwartz and Deczkowska, 2016). These findings together describe the relationship among gut dysbiosis-mediated amyloid-like deposition, defective autophagy, altered immune status, and NDD pathologies.

4. Gut dysbiosis in neurodegenerative diseases

Recent studies have shown that alteration of microbiota-gut-brain homeostasis is linked to pathogenesis and progression of NDDs (C et al., 2020; Patrick et al., 2019). Indeed, the increased intestinal and BBB permeability due to gut dysbiosis causes the translocation of gut microbes and their neuroactive metabolites, which induces toxic inflammatory milieu affecting the host immune homeostasis and altering brain morphology (Greco et al., 2019). The influence of gut dysbiosis on the pathophysiology of proteinopathies and their prion-like spread in NDDs including AD, PD, HD, AML, MS and FTLD are discussed below.

4.1. Alzheimer's Disease

Alzheimer's disease is a chronic age-related NDD characterized by a decline in cognitive function, memory, verbal and motor activities, termed dementia in older adults (Bishir et al., 2020; Wilson et al., 2010). Accumulation of Aβ as senile plaques (extracellularly) and hyper-phosphorylated tau protein as neurofibrillary tangles (intracellularly) are the main neuropathological toxins in AD (Ferreira et al., 2015; Medina and Avila, 2014). Several preclinical and clinical studies report the direct association of gut dysbiosis with the aetiology of AD (Bonfili et al., 2017; Hill and Lukiw, 2015; Hoffman et al., 2019). Recent studies suggest that Aβ proteins produced by the gut microbiota including *Streptococcus, Staphylococcus, Salmonella, Mycobacteria, Klebsiella, Citrobacter,* and *Bacillus* genera, can trigger protein misfolding into Aβ structures in the brain and enhance neuroinflammation (Sharon et al., 2016; Uesaka et al., 2016). Transgenic (TG) AD mice overexpressing amyloid precursor protein (APP) showed distinct alterations in gut microbiota composition and biodiversity (Harach et al., 2017). APP TG mice raised in germ-free (GF) conditions showed a drastic decrease in the level of cerebral Aβ pathology compared to WT control mice raised conventionally. APP TG-GF mice colonized with gut microbiota from conventional APP TG mice show an increase in cerebral Aβ pathology, while APP TG-GF mice that received gut microbiota from WT mice did exhibit enhanced levels of cerebral Aβ (Bauer et al., 2019). Similarly, mice overexpressing APP and PS1 (APP/PS1) showed an altered microbial composition, with a notable increase in the inflammatory related *Erysipelotrichacea*e family when compared to WT control mice (Radde et al., 2006). In addition, APP/PS1 mice demonstrated reduced levels of cerebral Aβ compared with conventional mice (Brandscheid et al., 2017), suggesting that gut dysbiosis may better enable the murine brain to handle the Aβ pathology. In contrast, GF APP/PS1 mice displayed higher levels of Aβ-, insulin- and neprilysin-degrading enzymes compared with conventional APP/PS1 mice (Harach et al., 2017). Moreover, 5xFAD mice (a transgenic model which recapitulates major features of AD amyloid pathology) showed elevated levels of human

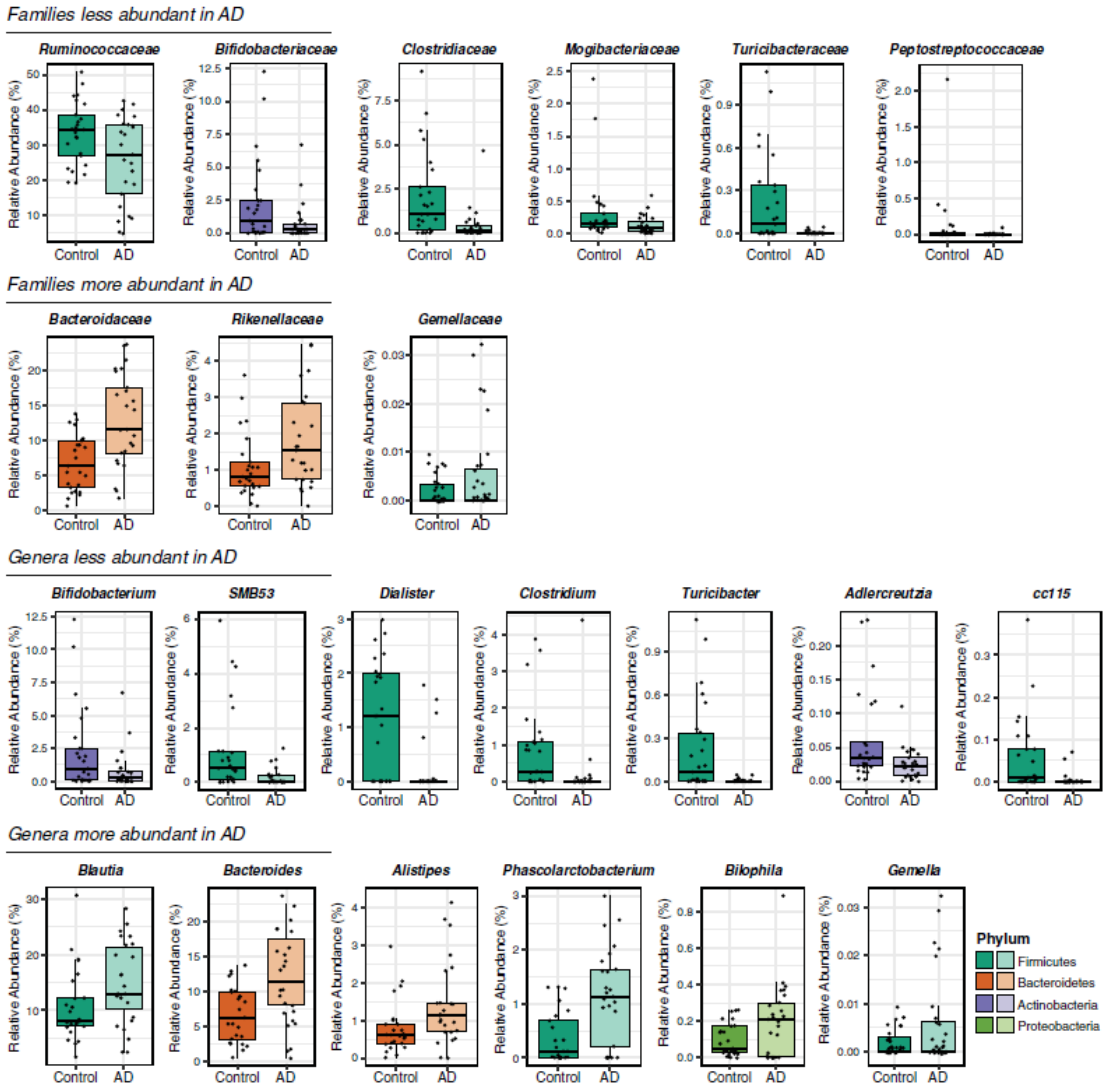
Aβ protein in the brain and GI tract along with an altered microbiota (elevated *Firmicutes* phyla and decreased *Bacteroidetes* phyla) compared to WT controls (Harach et al., 2017). Additionally, altered gut microbiota composition was also found in another well-characterized mouse model of symptomatic AD, Tg2576 mice (Brandscheid et al., 2017).

In another in vivo study (Kim et al., 2020), $ADLP^{APT}$ (a recently developed transgenic AD mouse model) mice showed Aβ plagues, neurofibrillary tangles, reactive gliosis in the brain with memory defects, a loss of intestinal barrier integrity, intestinal inflammation, and altered gut microbiota. These changes were ameliorated by faecal microbiota transplant (FMT) of the gut microbiota from healthy WT mice. Similarly, after treatment with broad-spectrum antibiotics, brain samples of APP/PS1 transgenic mice mimicking AD with gut dysbiosis ($APP^{swe}/PS^{\Delta E9)}$) (PAP) showed significantly reduced composition and diversity of the gut microbiota as well as SCFAs levels along with notable decreases in the levels of Aβ peptide, Tau protein, COX-2, CD11b, glial reactivity, and circulating cytokines and chemokines when compared with WT controls (Minter et al., 2016). In contrast, recolonization of GF mice with faeces of conventionally raised AD mice induces an increase in Aβ pathology (Harach et al., 2017). Similarly, APP/PS1 mice showed reduced microglial activation leading to elevated Aβ deposition, synaptic dysfunction, and neuroinflammation resulting in cognitive deficits vs. WT mice. However, TG mice that received FMT from WT mice show decreases in Aβ and tau protein levels, and improvement in the synaptic plasticity and alteration in gut microbiota composition as compared to WT mice (Sun et al., 2019). Furthermore, AD transgenic animals display impaired adaptive immunity, confirming that Treg cell activation modulates neuroinflammation in AD (Dansokho et al., 2016; Schwartz and Deczkowska, 2016). This evidence suggest that gut dysbiosis-mediated alterations can induce abnormalities in more than 30 different metabolic pathways, which is associated with Aβ deposition and ultrastructural abnormalities in the brain of AD patients (C. Zhang et al., 2017). Recolonization of the broad-

spectrum antibiotic-treated GF PAP mice with gut microbiota from conventional mice resulted in aggravated AD pathology (Harach et al., 2017). FMT from AD patients to GF mice worsened the cognitive functions and reduced the production of γ-aminobutyrate, taurine, and valine (Fujii et al., 2019).

Clinical studies have shown that brain samples of AD patients contain more pathogenic bacteria and LPS compared to controls (Fox et al., 2019; Hill et al., 2014). Both gut microbial richness and diversity are reduced in the elderly and in AD patients (Bostanciklioğlu, 2018). A recent study that analysed the gut microbiota composition of 25 AD patients reported a decreased microbial diversity that is taxonomically distinct from the asymptomatic age- and sex-matched controls, and the distinct microbial differences **(Fig. 3)**. Analysis at the phylum level showed a decreased abundance *of Firmicutes* and *Actinobacteria*, and increased abundance of *Bacteroidetes* compared to control participants (Vogt et al., 2017). Moreover, the most dominant phyla were *Firmicutes* (78%) and *Bacteroidetes* (15%), as well as the most dominant families were *Lachnospiraceae* (39.1%), *Ruminococcaceae* (29.6%) and *Bacteroidaceae* (9.8%). These changes strongly correlate with Aβ pathology and β-tau protein in the subgroup of patients **(Fig.4)**. Another clinical study (Cattaneo et al., 2017) reported the decrease in abundance of anti-inflammatory *Eubacterium rectale* and *Bacteroides fragilis* and increase in the abundance of the inflammatory taxon *Escherichia/Shigella* with higher levels of IL-1β, CXCL2, NLRP3, and Aβ peptide in elderly patients with amyloidosis when compared to healthy controls (HCs) and subjects with cognitive impairment but had no Aβ pathology. A subsequent study in AD patients reported that a reduction in *Bifidobacterium breve strain A1* abundance and an increase in *Escherichia/Shigella* abundance correlate positively with higher levels of proinflammatory cytokines (IL-1 and CXCL2), which can promote inflammation in the plasma and CNS (Kobayashi et al., 2018).

Another recent clinical study (Haran et al., 2019) confirmed these findings that elderly AD patients have a lower abundance of butyrate-producing bacteria (*Butyrivibrio*, *Eubacterium*, *Clostridium sp.* strain SY8519, *Roseburia hominis*, and *F. prausnitzii*) and a higher proportion of taxa that correlate positively with a proinflammatory state (*Bacteroides vulgatus*, *B. fragilis*, and *Eggerthella lenta*) and neurological disorders (*Odoribacter splanchnicus*). Moreover, stool samples of AD patients demonstrate lower levels of anti-inflammatory β-glycoprotein compared with samples from older adults without AD (Haran et al., 2019). Leblhuber et al., (2015) found signs of enteric inflammation in 22 AD patients along with higher level of calprotectin in their faecal samples. A significant increase in Aβ precursor protein, Aβ load, CD68, and β-Tau immunoreactivity in the intestine of AD patients and APP/PS1 mice suggest that the intestine may mimic the brain, and induce inflammation and dysregulated immune activation relating to Aβ precursor protein and Aβ pathology (Puig et al., 2015). Both the brain parenchyma and blood vessels of AD patients show higher levels of LPS and the *Escherichia coli* K99 pili protein, and colocalization of LPS with Aβ1-40 in amyloid plaques, which confirms the translocation of bacterial metabolites from gut to the brain via the systemic circulation (Zhan et al., 2016).



958

959 **Fig. 3:** Overview of the altered gut microbiota compositions observed in Alzheimer's disease (AD)-
960 associated bacterial taxa. The top 9 bacterial families showing significant differences between the AD
961 and control groups, include enriched abundance of families including *Rikenellaceae*, *Bacteriodaceae*,
962 and *Gemellaceae* and depleted abundance of families including *Ruminococcaceae*, *Bifidobacteriaceae*,
963 *Clostridiaceae*, *Mogibactericeae*, *Turicibacteriaceae*, and *Peptostreptococcaceae*. Analysis at the
964 genus level revealed that genera of *Bifidobacterium*, SMD53, *Dialister*, *Clostridium*, *Turicibacter*,
965 *Adlercreutzia* and cc115 are reduced, while genera including *Blautia*, *Bacteriodes*, *Alistipes*,
966 *Phascolarcbacterium*, *Bilophila* and *Gemella* are increased. The figure is reused as per journal
967 copyright permission (Vogh et al., 2016).

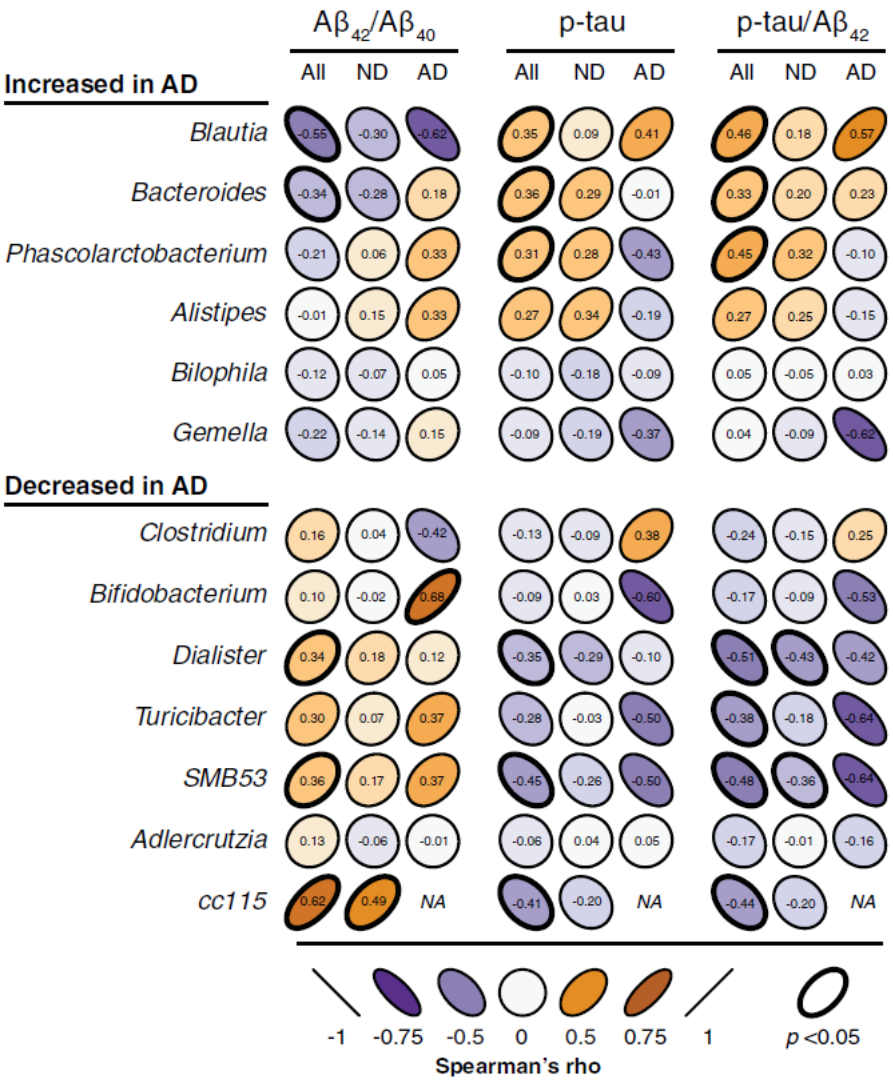


Fig.4 Diagrammatic demonstration on the correlation between bacterial taxa and CSF biomarkers of AD-related proteins Aβ and p-tau. The figure is reused as per journal copyright permission (Vogt et al., 2017).

Furthermore, gut dysbiosis increases gut permeability by reducing the expression of tight junction proteins in colonic epithelial cells ("Increased intestinal permeability and gut dysbiosis in the R6/2 mouse model of Huntington's disease | Scientific Reports," n.d.) leading to excessive circulating levels of microbes (such as spirochaete, Herpes simplex virus type 1 and *Chlamydia pneumoniae*) and microbial metabolites (BMAA, LPS and microbial amyloids) (Itzhaki et al., 2016; Ransohoff, 2016), which trigger systemic inflammation by increasing

levels of pro-inflammatory cytokines via iNOS (Tükel et al., 2009) and NF-κB (Tükel et al., 2010) signalling. Gut microbiota-derived amyloid may enhance inflammation in response to cerebral Aβ42 through the innate immune system (Friedland, 2015). Subsequently, aggravated systemic inflammation (Zhao et al., 2017) affects the BBB permeability leading to infiltration of pathobionts, microbial products and inflammatory mediators into the brain, and triggers inflammation by modifying microglial maturation (Erny et al., 2015; Thevaranjan et al., 2017) and astrocyte activation (Rothhammer et al., 2016), leading to neurodegeneration and neuronal death in AD patients (Dinan and Cryan, 2017; Morris et al., 2019). In support of this, BBB damage and accumulation of blood-derived products are evident in AD brains (Kowalski and Mulak, 2019). Furthermore, gut dysbiosis induced by an increase in proinflammatory gut bacteria, especially *Salmonella*, *Bacillus*, *Mycobacterium*, *E. coli*, and *Staphylococcus*, can induce neuroinflammation and aggravate cerebral Aβ deposition in AD patients (Pistollato et al., 2016). These results bolster the concept that gut dysbiosis has a strong link with AD pathogenesis. Reduced gut microbial diversity in patients modulates gut and brain homeostasis, triggering NDD pathologies including inflammation, Aβ aggregation and tau pathology via the dysregulated immune pathways (Zhuang et al., 2018). However, further studies are required to better understand the role of the gut microbiota on the GBA in AD.

4.2. Parkinson's disease

PD is the second most common NDD, and is characterized by both motor (slowness of movement, rigidity and resting tremor) and non-motor (cognitive decline, depression, alternations in mood, as well as sensory and sleep disturbances) (Nair et al., 2018; Kumar and Jangra, 2012; Sathiya et al., 2013). PD patients commonly report prodromal nonmotor-related symptoms 20 years before the onset of the motor symptoms including constipation, hypersalivation, dysphagia, delayed gastric emptying, nausea, constipation and altered bowel

habit (Aarsland et al., 2017; C et al., 2020). Accumulation of Lewy body (LB) deposits (mainly alpha-synuclein and ubiquitin) in the midbrain dopaminergic neurons, characterizes PD pathogenesis (Schneider and Alcalay, 2017). Both pathologic and epidemiologic studies have hypothesized that PD may start in the ENS and spread from gut via the vagus nerve and spinal cord to the brainstem (Brundin et al., 2010; Dugger et al., 2017). Indeed, animal models of PD show that the abnormal αSyn deposition begins in the olfactory bulbs and/or in the ENS (due to the exposure to environmental pathogens or gut dysbiosis). It then proceeds through the trans-synaptic transmission to the dorsal motor nucleus of the vagus nerve, and then from the vagus to the substantia nigra pars compacta of lower brainstem through retrograde axonal transport and onto further sites in the CNS (Peelaerts et al., 2015).

Several animal studies confirm that alterations in the gut microbiota and inflammatory state are important co-factors involved in PD pathology. Accordingly, elimination of the gut microbiota with antibiotics ameliorated PD pathology in a human αSyn over-expressing mouse model (Thy-αSyn). In contrast, GF mice that received FMT from PD patient donors showed disease progression with increased motor dysfunction and neuroinflammatory state, suggesting the presence of specific disease promoting microbes (Sampson et al., 2016). A recent study in a methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of PD indicates that changes in gut microbiota composition are reversed by FMT from healthy donors (Gorecki et al., 2019). Additionally, these PD mice show increased levels of SCFAs, striatal dopamine and 5-HT and reduced physical impairment. FMT also protects PD mice by reducing the activation of microglia and astrocytes, as well as TLR4/TNF-α signalling in gut and brain (Gorecki et al., 2019). Moreover, LPS-induced PD mouse models (T. Zhang et al., 2014) also showed increased levels of microglial activation, proinflammatory cytokine production, and haeme-oxygenase-1, and a decrease in the level of ferroprotein.

In support of these findings, other studies have shown that FMT from healthy donors (Sun et al., 2019, p. 1) and butyrate administration in animal models of PD improves motor impairment and dopamine deficiency (Liu et al., 2017; Paiva et al., 2017). Similarly, PD patients display LB deposits first in the olfactory epithelium (Saito et al., 2016) and in both submucosal and mucosal plexuses of the gut (from the oesophagus to the rectal end) in post-mortem cases of early PD. This observation reflects the preclinical stage of PD (Del Tredici et al., 2010), as LB pathology appears 20 years prior to PD diagnosis (H. Braak and Del Tredici, 2008; Heiko Braak and Del Tredici, 2008). Recent studies confirm the presence of abnormal αSyn in intestinal EECs (Chandra et al., 2017) and vagal afferents (Bohórquez et al., 2015). A higher prevalence of peptic ulcer and *Helicobacter pylori* infection were also reported in PD patients (Bjarnason et al., 2005) and the drug-induced eradication of *H. pylori* infection can ameliorate PD symptoms (Nielsen et al., 2012).

Parkinsonian patients also suffer gut microbiota alterations that correlate with disease progression, as there is a continuous decrease in fibre-degrading bacterial strains and an increase in pathobionts, which probably leads to a decrease in SCFA production and an increase in endotoxin and neurotoxin production (Li et al., 2017). Clinical analysis of faecal samples reveals significant alterations in gut microbiota composition with reduced abundance of *Bacteroidetes* and *Prevotellaceae,* in contrast to higher abundance of *Enterobacteriaceae* and *Lactobacillaceae* in PD patients (Hopfner et al., 2017; Scheperjans et al., 2015) when compared to age matched controls, which correlate positively with increased postural instability and distinctive gait (Unger et al., 2016). A subsequent study reveals that both sigmoid mucosal and faecal microbial composition show a higher abundance of proinflammatory-associated bacteria of the genera *Ralstonia* and *Faecalibacterium,* and lower abundance of anti-inflammatory-associated bacteria from the genera *Blautia*, *Coprococcus,* and *Roseburia,* as well as butyrate-producing bacteria, corresponding to the inflammation-

related misfolding of αSyn and pathology of PD in CNS (Keshavarzian et al., 2015). A reduction of *Lachnospiraceae* leads to a more severe impairment of motor and non-motor symptoms in PD patients (Barichella et al., 2019). In addition, increased abundance of mucin-degrading *Verrucomicrobiae* and LPS-producing *Gammaproteobacteria* was noted in both PD patients and a Thy1-αSyn mouse model as compared to healthy and WT controls (Gorecki et al., 2019). A recent study confirms that PD patients showed increased α-diversity indexes (measures the microbial diversity within each sample) compared to healthy spouse and healthy participant (HP) groups. Beta diversity analysis (which measures differences between samples) exhibited a distinct separation between the PD patient and two healthy groups. The relative abundance of *Firmicutes*, *Actinobacteria* and *Verrucomicrobia* phyla were significantly higher in PD samples than in the healthy groups; the relative abundance of *Bacteroidetes* and *Fusobacteria* were significantly lower in the PD group compared with healthy groups. At the genus level, *Oscillospira* and *Akkermansia* were significantly higher in PD patients than the healthy groups, but *Fusobacterium* was significantly lower in PD samples than the healthy groups. The relative abundance of *Prevotella* was lower in PD samples compared with HP samples, but similar to the abundance noted in healthy spouse samples. LEfSe analysis identified 33 gut bacterial markers which could discriminate PD patients from healthy groups, which included 25 and 8 enriched bacterial taxa in the PD and healthy samples, respectively (Zhang et al., 2020) **(Fig. 5)**.

Furthermore, PD patients display increased colonic expression of TLR4, CD3+T cells, and cytokines and decreased abundance of SCFAs producing bacteria. Similarly, rotenone treatment reduced and/or reversed similar gut and neurological disorders in TLR4-knockout mice (Perez-Pardo et al., 2019). Colonic biopsies of PD patients show increased mRNA expression of pro-inflammatory cytokines as compared to controls (Devos et al., 2013). Altogether, these results suggest that consistent interaction between the gut microbiota and its

metabolites with TLRs, neuroinflammation and αSyn pathology, synergistically contribute to the neurodegeneration in PD (Rietdijk et al., 2016). Thus, halting TLR engagement via gut microbiota modulation may be an important therapeutic target in the treatment of PD (Drouin-Ouellet and Cicchetti, 2012).

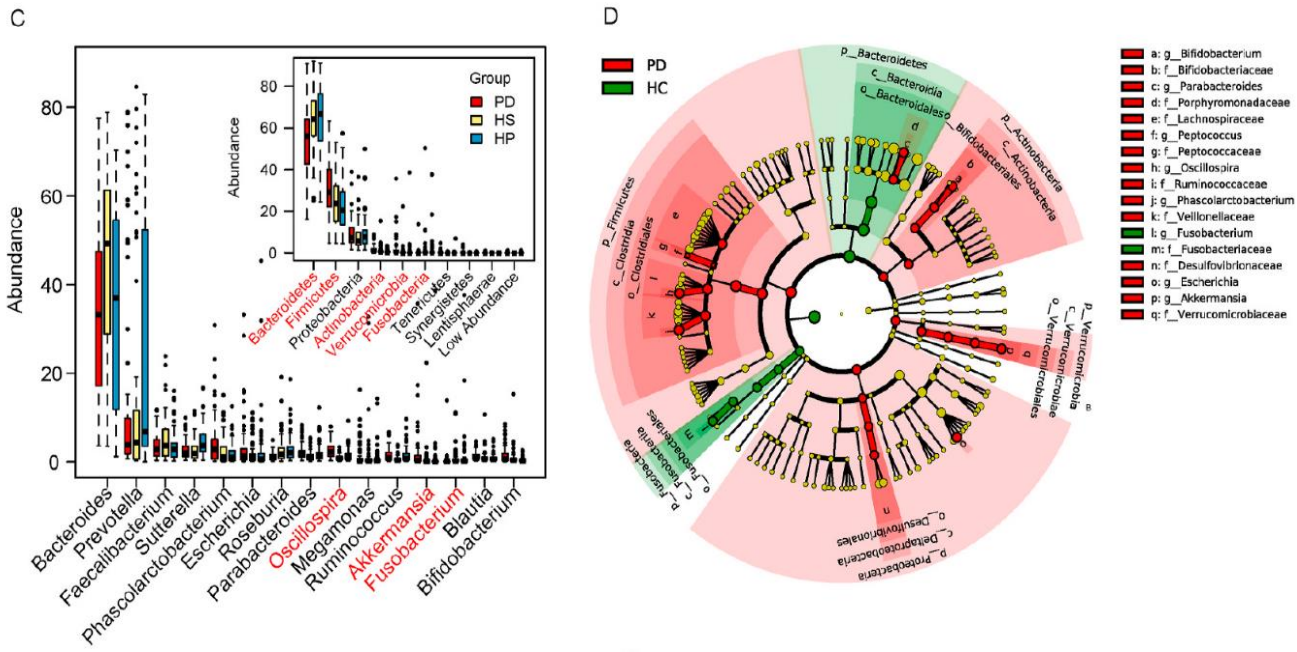
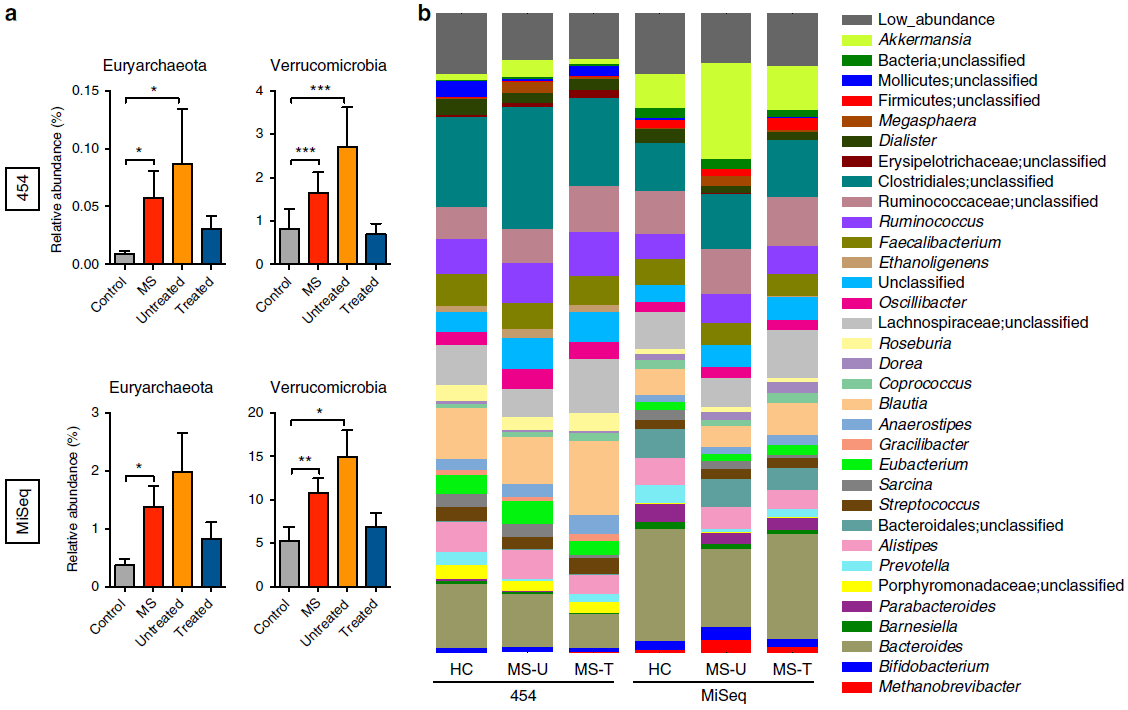


Fig. 5: Altered gut microbiota composition in patients with Parkinson's disease (PD): (C) The most important (10 abundant) phyla and (15 abundant) genera in PD, healthy spouse (HS) and healthy participant (HP) samples are graphed from higher to lower abundance. (D) LEfSe analysis of 33 significantly differential bacterial taxa in the PD (red) compared to HC (green) groups. The figure is reused as per journal copyright permission (Zhang F et al., 2020).

4.3. Multiple sclerosis

MS is a chronic autoimmune NDD caused by progressive immune-mediated demyelination, axonal damage and neurodegeneration. Clinically, MS is characterized by sensory, visual, autonomic, and cognitive impairment along with ataxia, muscle spasms, paralysis, bladder and bowel dysfunction, and fatigue (Dendrou et al., 2015; Ramagopalan et al., 2010). Recent evidence indicates that gut dysbiosis is one of the prime factors responsible for MS neuropathogenesis (Bhargava and Mowry, 2014; Mowry and Glenn, 2018). Specifically, the relapsing/remitting form of MS (RRMS) is characterized by decreased abundance of anti-

inflammatory bacteria as well as increased abundance of pro-inflammatory bacteria, through regulation of immune cells including Treg cells, IL-10-secreting CD4+ T cells, regulatory B cells, tolerogenic DCs and suppressive macrophages (Shahi et al., 2017). Several clinical studies report that the gut microbial profile of MS patients was different from healthy individuals (J. Chen et al., 2016; Jangi et al., 2016). Patients with RRMS show decreased abundance of *Parabacteriodes distasonis* (Cekanaviciute et al., 2016), *Faecalibacterium* (Mowry and Glenn, 2018) and *Prevotella copri* (Miyake et al., 2015) when compared with HCs. RRMS patients show an increased abundance of *Pseudomonas, Mycoplana*, *Haemophilus*, *Blautia*, and *Dorea* genera, while age- and gender-matched HCs show increased abundance of *Parabacteroides*, *Adlercreutzia* and *Prevotella* genera (J. Chen et al., 2016). Genera including *Faecalibacterium, Prevotella, and Anaerostiples* are significantly reduced in MS patients (Miyake et al., 2015). Patients with MS have a significantly increased relative abundance of the phyla *Euryarchaeota* and *Verrucomicrobia* compared to HCs (Jangi et al., 2016) **(Fig. 6)**. The relative abundance of genera including *Methanobrevibacter, Acinetobacter calcoaceticus* (Cekanaviciute et al., 2016) and *Akkermansia muciniphila* are increased, while *Collinsella*, *Sutterella* and *Slackia* are decreased in MS patients compared to HCs (Jangi et al., 2016). Additional studies in paediatric MS patients show greater colonization of *Firmicutes* when compared to healthy children, while depletion of specific gut flora and their metabolites are associated with an increased risk of relapse (Tremlett et al., 2016; Tremlett and Waubant, 2018). Higher levels of circulatory Th1 and Th17 cells increase BBB permeability and induce inflammation in the CNS (Dendrou et al., 2015).



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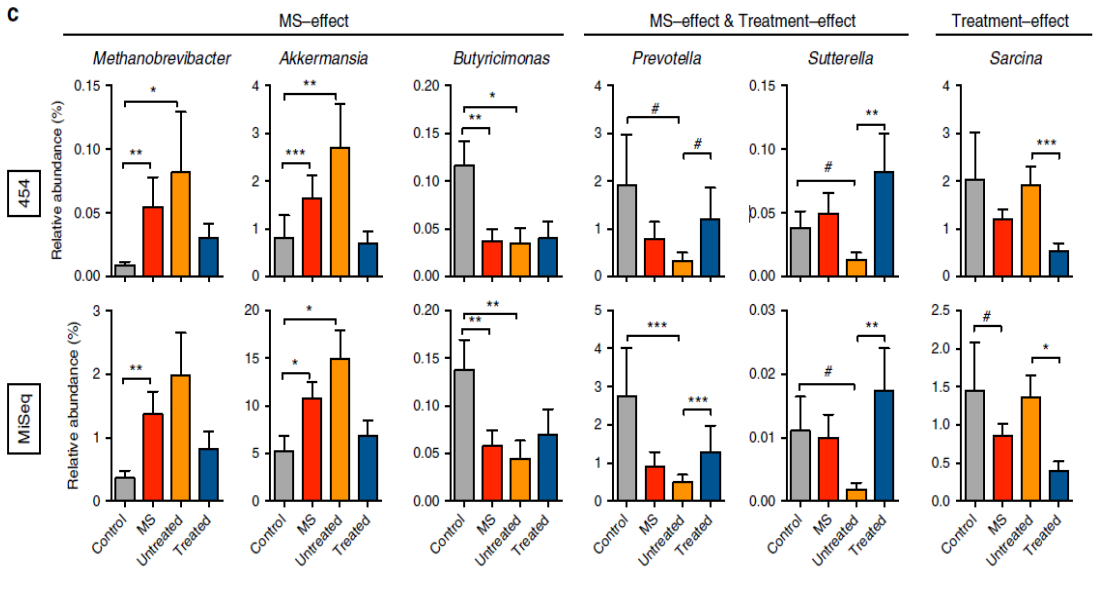

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1125 **Fig. 6:** Altered gut microbiota composition in multiple sclerosis (MS) subjects at the phyla and
1126 genus levels analysed by Roche 454 and Illumina sequencing. Data revealed that MS patients
1127 show increased abundance of the phyla Euryarchaeota and Verrucomicrobia compared to
1128 healthy controls (6a, b). The relative abundances of *Methanobrevibacter* (a genus in the
1129 phylum Euryarchaeota) and *Akkermansia* (a genus in the phylum Verrucomicrobia) were
1130 increased in MS patients compared with controls (6c). The figure is reused as per journal
1131 copyright permission (Jangi S et al., 2016).

1132

Preclinical studies using GF mice and experimental autoimmune encephalomyelitis (EAE), a murine model for MS, have provided greater insights into the contribution of gut microbiota changes in leading to the observed pathology in MS. GF mice show higher expression of myelin-related genes (such as *Mag*, *Mbp*, *Mog*, and *Mobp*) in the prefrontal cortex relative to conventional mice, which returned to control levels after recolonization with gut microbiota (Hoban et al., 2016). Antibiotic treatment also increased the expression of myelin-related genes in the prefrontal cortex of non-obese diabetic mice (Gacias et al., 2016). Transgenic SJL/J mice (a relapsing–remitting mouse model of spontaneous EAE) raised in GF conditions are protected against developing EAE (Berer et al., 2011) and show significantly attenuated EAE scores relative to conventional controls, due to a reduced ability of DCs to activate proinflammatory T cells (Lee et al., 2011). In the absence of a complex microbiota, activation of IFN-γ and IL-17-producing Th1 and Th17 cells is blunted together with enhanced recruitment and proliferation of Foxp3+ Treg cells (Ivanov et al., 2009). In contrast, introduction of commensal microbiota into the gut reverses susceptibility to EAE in transgenic SJL/J mice (Berer et al., 2011). Specifically, recolonization of GF mice with segmented filamentous bacteria alone restored the levels of Th17 cells in CNS and generation of IL-17 in the gut resulted in the development of EAE, thus confirming the role of gut microbiota in modulating the proinflammatory status of the brain in EAE (Ivanov et al., 2009). Mono-colonization of the gut of C57BL/6 mice with segmented filamentous bacteria promotes Th17 accumulation in the spinal cords and induced the development of EAE (Lee et al., 2011) . Conversely, treatment of C57BL/6 mice with a polysaccharide from the organism *Bacteroides fragilis* expands intestinal Foxp3+ CD4 Treg cells and protects against the development of CNS autoimmunity (Ochoa-Repáraz et al., 2009; Round and Mazmanian, 2010) . Gnotobiotic mice transplanted with faecal microbiota from MS patients develop spontaneous EAE and show a more severe form of disease than gnotobiotic mice transplanted with faecal microbiota from healthy mice (Berer et

al., 2017). Similarly, GF-C57 mice that received FMT from MS patients suffer a significantly more severe form of EAE, while those that received FMT from healthy individuals develop mild EAE, when compared with controls (Cekanaviciute et al., 2017). Recently, antibiotic-induced microbiota depletion in a mouse EAE model was shown to prevent motor dysfunction and axon damage, while recolonization with the microbes restored the susceptibility to EAE through the involvement of T cells (CD4+ and CD39+) and B cells (CD1d+ and CD5+) (Mestre et al., 2019). Similarly, antibiotic treatment delays the onset of clinical symptoms by decreasing the level of IFN-γ and IL-17A and increasing the level of IL-10 in serum of EAE mice. Furthermore, antibiotic treatment decreases brain-derived neurotrophic factor (BDNF) and increases TNF-α and IL-1β in the hippocampus of EAE mice. In addition, antibiotics also decrease depression-related symptoms, whilst increasing anxiety-like behaviour as well as improving learning and memory (Zeraati et al., 2019). Rats which exhibit a higher diversity of *Lactobacillus* species are found to be more resistant to develop EAE than those rats with lower diversity of the lactic acid bacteria, suggesting that enriching the gut microbiota using beneficial *Lactobacillus* strains may be used as a preventative measure for MS (Stanisavljević et al., 2016). Treatment of Lewis rats with *Bifidobacterium animalis* (Ezendam et al., 2008) and mice with a mixture of *Lactobacillus spp.*(Lavasani et al., 2010) regulate the level of CNS inflammation and clinical scores in EAE. Treatment with probiotic VSL3 enriches beneficial microbes in the large intestine and inhibits peripheral inflammation mediated by monocytes, but these anti-inflammatory effects disappear after discontinuation of VSL3 (Tankou et al., 2018a). Collectively, these studies confirm the association of the gut microbiota on NDD at clinical and preclinical levels in MS. Thus, targeting the modulation of specific microbiota either by subtle dietary changes or probiotics may potentially contribute to the treatment and prevention of relapse in MS patients.

4.4. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive loss of upper and lower motor neurons in the motor cortex, brainstem, and spinal cord, leading to progressive paralysis, muscle weakness and body weight loss (Brown and Al-Chalabi, 2017). Mutations in Cu/Zn-superoxide dismutase 1 (SOD1) (Münch et al., 2011), TDP-43 and fused in sarcoma/translated in lip sarcoma (FUS/TLS) are the common causes for the familial type of ALS (Pasinelli and Brown, 2006). The principal component of misfolded protein is ubiquitinated cytoplasmic inclusions found in neurons and glia in ALS (Jeon et al., 2019). Pathogenesis implicates glutamate excitotoxicity, severe mitochondrial dysfunction, redox imbalance, changes in the RNA metabolism, microglial and astrocyte activation, and autophagy dysregulation (Greco et al., 2019; McCombe et al., 2020). Recent studies show a strong pathophysiological interlink between gut dysbiosis and ALS (McCombe et al., 2019; Wright et al., 2018). Specifically, ALS pathogenesis is linked to the alterations in gut microbiota composition, impaired metabolism, altered innate immune response, and production of gut-derived neurotoxins (tetanus and botulinum toxins) by *Clostridia* species that induce brain damage (McCombe et al., 2019).

Preclinical studies of gut dysbiosis in ALS pathology show a clear dysfunction in the GI tract in a transgenic mouse model for ALS (SOD1G93A) compared to WT mice. Intestinal cells show a defective tight junction structure along with a reduced expression of the related protein (ZO-1), which correlates with increased permeability, enabling the passage of toxins from intestinal lumen into systemic circulation (Wu et al., 2015). Similarly, transgenic SOD1G93A mice show gut dysbiosis and altered metabolite configuration, even before the onset of motor symptoms (Blacher et al., 2019). Antibiotic treatment worsens disease severity under GF conditions. Alteration in abundance of strains such as *Parabaceroides distasonis, Lactobacillus gasseri, Prevotella melaninogenica, Ruminococcus torques*, and *Akkermansia muciniphila* promote increased disease severity. Specifically, the abundance of *A. muciniphila* is found to

decrease in a time-dependent manner with disease progression. Moreover, supplementation with *A. muciniphila* ameliorates ALS symptoms, while *R. torques* and *P. distasonis* exacerbates ALS symptoms in transgenic mice. Supplementation with 2% butyrate in drinking water in an ALS mouse model improves the gut integrity and survival (Y.-G. Zhang et al., 2017). These studies suggest that gut dysbiosis may have a direct role in ALS pathology.

A metagenomics study (Fang et al., 2016) reports that ALS patients have reduced *Firmicutes/Bacteroides* (F/B) ratio (an indicator of gut dysbiosis) together with a significantly increased abundance of *Dorea* and a decreased abundance of genera *Oscillibacter, Anaerostripes and Lachnospiraceae* vs. HCs. Similarly, another study (Rowin et al., 2017) reported a low abundance of *Ruminococcus*, and low F/B ratio in ALS patients compared to HCs, with most patients showing increased inflammatory markers such as faecal secretory IgA, eosinophilic protein X, and calprotectin, suggesting that gut-mediated inflammation is most likely to be involved in ALS onset or progression. Conversely, quantitative PCR analysis reveals a higher abundance of *Escherichia coli* and *Enterobacteria*, and a lower abundance of *Clostridium* and yeast in ALS patients (Mazzini et al., 2018), confirming that an imbalance in gut microbiota constitution has a strong association with ALS pathogenesis. A recent prospective longitudinal study reports an imbalance between the protective antimicrobial groups (*Bacteroidetes*) and proinflammatory groups (*Cyanobacteria*) in ALS patients, along with a higher abundance in *Enterobacteriaceae, Akkermansia, Eubacterium, Prevotellaceae and Ruminococcaceae* families. In contrast, controls show a higher abundance of genera of the *Veillonellaceae* and *Lachnospiraceae* families (the genus *Parasutterella, Ruminococcus and Subdogranulum*). Other faecal microbiota studies have detected higher abundance of *Bacteroidetes* at phylum level and *Kineothrix, Parabcateroides, Odoribacter, Sporobacter, Eisenbergiella, Mannheimia, Anaerotruncus*, and unclassified *Porphyromonadaceae* in ALS patients compared to controls (Zeng et al., 2020). In contrary, ALS patients display a significant

reduction in *Firmicutes* at phylum level and at *Megamonas* at the genus level vs. control group. A comparative study (Zhai et al., 2019) also reported that ALS patients show a relatively higher F/B ratio at the phylum level, in contrast to lower levels of beneficial bacteria such as *Faecalibacterium* and *Bacteroides*, as compared to healthy individuals. However, more clinical evidence is warranted to clarify how the gut microbiota improves or aggravates ALS.

4.5. Huntington's disease

Huntington's disease (HD) is a progressive NDD caused by an unstable expansion of trinucleotide (cytosine-adenine-guanine) repeat in the *huntingtin* gene (Htt) that is expressed ubiquitously in the brain and peripheral tissues (MacDonald et al., 1993). Characteristic clinical features include a triad of cognitive, psychiatric and motor impairments, as well as unintended weight loss (Wasser et al., 2020), skeletal muscle atrophy, and GI dysfunction (Andrich et al., 2009; van der Burg et al., 2011). Early pathological features of the HD in both patients and animal models reveal neuronal degeneration in the basal ganglia, white matter atrophy, and myelination deficits (Shaffer et al., 2017; Teo et al., 2019). Further, the presence of the mutant protein in the ENS and IECs, leads to the loss of gut-derived neuropeptides, which correlates with gut dysfunction (van der Burg et al., 2011). Circulating gut metabolites were altered in HD patients and transgenic animals, suggesting that the gut microbiota could be altered even before the disease onset (Verwaest et al., 2011). Furthermore, unintended weight loss has been induced by GI dysfunction in a HD mouse model (van der Burg et al., 2011). A recent study in R6/1 transgenic mouse model of HD reported an altered gut microbial composition at 12 weeks of age, especially, an increase in level of *Bacteroidetes* and a decrease in the level of Firmicutes. Gut dysbiosis was found to be correlated with impairment in body weight gain despite higher food intake and motor deficits (Kong et al., 2020) .

Another R6/2 mouse model of HD study (Stan TL et al., 2020) showed that increased intestinal permeability and gut dysbiosis was accompanied by a significant reduction in colon length compared to wild type littermates. Moreover, gut microbiota of R6/2 mice showed increased relative abundance of *Bacteroidetes* and decreased relative abundance of *Firmicutes*. At 18 weeks of age, the colon mucosa of R6/2 mice showed lower expression of occludin and disrupted epithelial organization, whereas there was a strong expression of mucosal occludin and intact epithelium in wild type mice. Patients with HD were found to have significant differences in the gut microbial communities (beta diversity) and showed a significant decrease in species richness and evenness (alpha-diversity) between combined HD gene expansion carrier group and healthy controls (Wasser et al., 2020). For example, *Euryarchaeota*, *Firmicutes*, and *Verrucomicrobia* phyla were notably different between male groups. At the family level, *Acidaminococcaceae, Akkermansiaceae, Bacteroidaceae, Bifidobacteraceae, Clostridiaceae, Christensenellaceae, Coriobacteriaceae, Eggerthellaceae, Enterobacteriaceae, Erysipelotrichaceae, Flavobacteriaceae, Lachnospiraceae, Methanobacteriaceae, Peptococcaceae, Peptostreptococcaceae*, and *Rikenellaceae* were also significantly different between male groups.

5. The role of short-chain fatty acids in neurodegenerative diseases

SCFAs serve as an energy source and also possess neuroactive and immunomodulatory properties (Stilling RM et al., 2016, Dalile B et al., 2019). Moreover, SCFAs influence host cells through a variety of mechanisms, including altering histone acetylation and cell proliferation, and activation of G-protein coupled receptors. Reduction of SCFA-producing bacteria are reported in several cardiovascular, neuropsychiatric and metabolic disease models, including stroke, hypertension, obesity, and diabetes mellitus (Durgan DJ et al., 2016; Yang T et al., 2015; Spychala MS et al., 2018). Several studies have shown that restoration of optimal

levels of SCFAs and healthy gut microbiome effectively reduced neurodegenerative pathology. Alterations of the epigenome have been documented in a variety of brain disorders, including neurodevelopmental, psychiatric, and neurodegenerative diseases (Liu and Jaenisch., 2019; Basavarajappa and Subbanna., 2021; Ghosh and Saadat., 2021). The role of SCFAs in NDDs like AD, PD, AML and MS are discussed in detail below.

In AD, SCFAs disrupt the assembly of amyloid-beta (Aβ) oligomers into neurotoxic aggregates, by interfering their protein-protein interactions Aβ peptides (Ho L et al., 2018). Likewise, reestablishment of a healthy gut microbial community in APP/PS1 mice by fecal microbiota transplantation (FMT) from healthy wild-type mice, significantly reduced cognitive deficits, Aβ accumulation, synaptic dysfunction, and neuroinflammation, mainly by SCFAs-mediated microglia homeostasis (Sun J et al., 2019). Similarly, treatment of the young 3xTg mouse model of AD with probiotics revealed a reduction in inflammatory cytokines and cognitive impairment associated with reduced brain damage and Aβ aggregate accumulation (Bonfili L et al., 2017). Further, butyrate administration (via histone inhibition) reduced memory deficit and increased expression of genes implicated in associative learning in the APP/PS1 mouse model of AD (Govindarajan N et al., 2011). Treatment with prebiotic fibres such as inulin and fructo-oligosaccharides (FOS) promote the growth of butyrate-producing bacteria such as *Clostridium*, *Eubacterium*, *Fusobacterium*, *Roseburia,* and *Faecalibacterium* genera (Fu et al., 2019). Thus, these microbes secrete high levels of butyrate, which exhibits neuroprotective, cognitive and anti-depressive effects (Dalile et al., 2019).

In patients with Parkinson's disease (PD), Li and colleagues confirmed that gut dysbiosis correlate positively with disease progression, along with a constant reduction in fiber-degrading bacterial microbes and an increase in pathobionts, which is reflected by the reduction of SCFA production and an increase in production of endotoxin (Li W et al., 2017). Studies show that FMT from healthy donors (Sun MF et al., 2018) in clinical models as well as butyrate

administration in animal models of PD reduced the motor deficit and dopamine deficiency (Liu et al., 2017).

In multiple sclerosis, oral supplementation of SCFAs reduced disease severity in experimental autoimmune encephalomyelitis (EAE) in an animal model of MS (Mizuno M et al., 2017). Specifically, acetate administration increased acetyl-CoA metabolism, which directly increases histone acetylation, leading to the maintenance of lipid content in the spinal cord and ultimately preventing the onset of clinical symptoms of EAE (Chevalier AC and Rosenberger TA, 2017). Moreover, butyrate treatment reduces demyelination and increases remyelination by promoting the maturation and differentiation of oligodendrocytes (Chen T et al., 2019).

Clinical and animal studies of amyotrophic lateral sclerosis (ALS) subjects showed increased relative abundance of pathobionts (Clostridia species producing tetanus and botulinum toxins) than beneficial microbes (butyrate-producing bacteria) than healthy subjects, suggesting that anti-inflammatory SCFAs produced by GM are retard ALS progression (Mazzini L et al., 2017; Zhai CD et al., 2019). Oral butyrate supplementation (2% in drinking water) improved gut integrity and survival of an ALS mouse model (Zhang YG et al., 2017).

6. Potential therapeutic strategies in neurodegenerative diseases

Recent preclinical and clinical studies have provided scientific evidence of the role of gut microbiota perturbation in NDD pathology, suggesting that targeting gut dysbiosis through prebiotics, probiotics, synbiotics or dietary interventions may be an effective strategy for treating symptoms in mood-related , neurodevelopmental and neurodegenerative disorders (Stilling and Cryan, 2016). A complementary diet-based preventive and therapeutic intervention in NDDs, focused on the modulation of gut microbiota composition and gut microbiota-derived metabolites, may serve as promising approaches to halt or slow down the

neuroinflammatory and degenerative processes in NDDs through establishing eubiosis (Borre et al., 2014; Cryan and Dinan, 2012; Harding et al., 2017). Current therapeutic approaches under consideration include modifying the existing microbial composition in the gut by dietary plans and/or administration of pre-, pro-, and post-biotics, (S. G. Chen et al., 2016; Kobayashi et al., 2019; Wang et al., 2015) or through FMT (Baquero and Nombela, 2012). Such interventions can provide positive effects by reversing gut dysbiosis towards a healthy state by reducing gut permeability, OS and intestinal inflammation. **Table 1** summarises ***specific non-pharmacological nutritional interventions and the use of prebiotics, synbiotics and probiotics*** (Wang et al., 2015) ***and faecal microbiota transplantation from healthy controls***

Table.1 Neuroprotective effects of specific nutritional intervention approaches in NDDs and neuropsychiatric disorders

CNS-related disorders	Types of study	Therapeutic interventions	Therapeutic outcomes	References
AD and PD	Specific nutritional intervention study	Caloric restriction	Exert neuroprotective effects by reducing the OS, NF-kB-dependent neuroinflammation and activity of pro-apoptotic factors as well as inducing autophagy.	(Maalouf et al., 2009; Shirooie et al., 2018)
LPS-induced Parkinsonian models and non-obese diabetic mouse models	Specific nutritional intervention study	Intermittent fasting	Rapidly enhance the growth of beneficial and anti-inflammatory microbes and also stimulates a beneficial change in levels of SCFAs.	(Tanca et al., 2018; Z. Zhang et al., 2014)
AD and PD	Ketogenic diet study	Ketogenic diet (diet with rich fat, moderate proteins and very little carbohydrate content) such as medium-chain	Parkinsonian symptoms improved by 43% in PD patients. Improved cognitive functions in AD patients.	(Reger et al., 2004; Vanitallie et al., 2005; Włodarek, 2019)

		triglyceride (beta-hydroxybutyrate)	Mainly, ketogenic diet diminishes the production of ROS in isolated mitochondria increased glutathione peroxidase activity.	
Mouse models of PD, AD, synucleinopathy and aging.	Specific nutritional intervention study	Ketogenic diet mediated higher intake by polyunsaturated fatty acids	Exerts neuroprotective effects by reducing mitochondrial dysfunction, motor defects, αSyn accumulation and inflammation.	(Afshordel et al., 2015; Coulombe et al., 2018; Perez-Pardo et al., 2019)
AD model	In vitro study	Grape seed polyphenolic bioactive like 3-hydroxybenzoic acid and 3-(3-hydroxyphenyl) propionic acid	Prevents the formation of neurotoxic aggregates, suggesting that a polyphenol-rich diet may attenuate amyloid accumulation in the brain.	(Wang et al., 2015)
PD model	In vitro murine study	Panax notoginseng extract	Suppress the microglial activation and decrease the release of	(Beamer and Shepherd, 2012)

			inflammatory cytokines (IL-6 and TNF-α)	
Hemi-parkinsonian rat model	In vivo study	The flavonoid Silymarin (extracted from the seeds and fruit of *Silybum marianum*)	Suppresses TLR4 activation, increasing anti-oxidant defenses, preventing apoptosis and alleviating nigral injury in the 6-OHDA-induced hemi-parkinsonian rats.	(Haddadi et al., 2018)
Depressive disorder	Clinical study	Polyunsaturated fatty acids, such as eicosapentaenoic acid and folate-based N-acetylcysteine	Effective and strongest adjuvant treatment in depressive patients.	(Firth et al., 2019)

6.1. Specific nutritional interventions

It includes caloric restriction (CR), either through reducing daily caloric intake or following intermittent fasting (Fontana, 2018). The neuroprotective effects of CR include anti-oxidant, anti-inflammatory and anti-apoptotic mechanisms (Shirooie et al., 2018). Fasting mainly exhibits protective effects by achieving eubiosis and restoring the levels of microbial-derived metabolites (Tanca et al., 2018; Z. Zhang et al., 2014).

Studies have been conducted to elucidate the role of ketone bodies such as acetoacetate and β-hydroxybutyrate (βHB) due to their structural similarity with SCFAs, during energy restricted metabolic states, such as caloric restriction and intermittent fasting. Recent findings suggest that ketone bodies coordinate cellular functions via novel epigenetic modification -β-hydroxybutyrlation that integrates the classic DNA methylation and histone covalent posttranslational modifications (PTM), including histone lysine acetylation, methylation and histone phosphorylation and ubiquitination (Dabek et al., 2020). Likewise, these studies have shown that fasting influences the gene and protein expression of several H^+-dependent monocarboxylate transporters, which alters the SCFAs absorption in the GI tract and their transmission to the brain (Schutkowski A et al., 2014). These transporters regulate the direction of energy supplies to important tissues during fasting. For example, butyrate promotes the secretion of growth hormone in pituitary cells via GPR41/43 activation and intracellular accumulation of Ca^{2+} (Miletta et al., 2014), suggesting that butyrate can act as a secondary mediator of metabolic adaptations of growth hormone during fasting, mainly by increasing lipolysis and protein retention.

Ketogenic diet [diet with rich fat, moderate proteins and very little carbohydrate content] has the potential to reduce neurodegeneration (Włodarek, 2019). Ketogenic diets are clinically beneficial in common NDDS, with promising early data from limited human trials (discussed

in section 5). Although it is not clear whether the benefits of a ketogenic diet are derived from the ketones themselves or other aspects of the diet, there is a high probability that at least some of the benefits are derived from βHB. βHB acts as an alternative circulating source of energy in the fasting state and has a direct epigenetic effect via βHB (Dowis and Banga., 2021). For example, βHB suppresses HDAC-induced oxidative stress and induces microglia to adopt the anti-inflammatory M2 morphology, and additionally can inhibit the proinflammatory NLRP3 inflammasome by altering potassium flux (Youm et al., 2015; Norwitz et al., 2020). Ketogenesis also activates metabolically protective γδ T cells in visceral adipose tissue that can restrain adipose tissue inflammation (Golberg EL et al., 2020) and leads to a reduction in Th17 cells in human and mice exposed to ketogenic diet (Ni et al., 2016; Kim et al., 2012).

Although, specific nutritional interventions provide neuroprotective effects, further studies are warranted to identify the specific pathways by which these strategies influence GBA signalling **[Text Box-3]**

Text Box-3

KEY DEFINITIONS

- **Gut eubiosis** refers to the restoration of healthy gut microbiome by treatment.
- **Psychobiotics** are targeted microbiota interventions in the form of prebiotics, probiotics or synbiotics that restore the healthy GM and support good mental health (Cryan and Dinan, 2012).
- **Probiotics** - A living microorganism that when ingested by humans or animals confers a health benefit (Sarkar et al., 2016).
- **Prebiotics** - A non-digestible short-chain carbohydrates which on ingestion selectively, stimulates the growth of particular classes or species of beneficial microorganisms (Sarkar et al., 2016).

- **Synbiotics** - A synergistic combination of both prebiotics and probiotics.
- **Faecal Microbiota Transplantation (FMT)** refers to the transplantation of entire microbial communities or portions of microbial communities from the donors of healthy humans, aimed at reversing dysbiosis in the host.

6.2. Probiotics, Prebiotics and Synbiotics

Species of the genera *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Enterococcus* are common examples of probiotics (Kuneš et al., 2016). Supplementation with probiotic mixtures (commonly, Bifidobacteria, Streptococci and *Lactobacilli*) is one of the most promising treatment approaches for ameliorating neuro-behavioural symptoms and bowel dysfunction (Fattorusso et al., 2019). Probiotics improve intestinal and immune homeostasis by restoring the gut microbiota (Azad et al., 2018; Reid et al., 2011), and exhibit neuroprotective effects in CNS disorders, by enhancing the production of neurotransmitters, such as glutamate and GABA, as well as brain-derived neurotrophic factor (BDNF) levels (Lu et al., 2008), including normalization of anxiety and depression-like behaviours (Abildgaard et al., 2017; Bravo et al., 2012) and by a reduction of autism spectrum disorder (ASD) (Rao et al., 2009). A meta-analysis of randomized controlled trials showed that probiotics improved cognitive functions in AD by reducing the levels of inflammatory and oxidative markers (Den et al., 2020).

Major prebiotics include lactulose, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), oligofructose and inulin (Iannitti and Palmieri, 2010). Prebiotics normalize the composition of beneficial bacteria including *Lactobacillus*, *Bacteroides*, and *Bifidobacterium* (Akbari et al., 2016; Vulevic et al., 2015), thus benefiting the GBA (Depeint et al., 2008), can improve brain functions and may also prevent neurological disorders such as AD (Kinney et

al., 2018), dementia (Li et al., 2017), IBS (Ng et al., 2018), PD (Rocha et al., 2015) and ASD (Siniscalco et al., 2018) **(Table 2)**.

Table.2 Neuroprotective effects of probiotics, prebiotics, synbiotics and FMT in neurodegenerative and neuropsychiatric disorders

CNS-related disorders	Types of study	Therapeutic interventions	Therapeutic outcomes	References
ASD	A randomized, double-blind, placebo-controlled study	Oral administration of probiotic *L. plantarum* PS128 for four weeks	Significantly improvement in ASD-related symptoms compared to the placebo treatment	(Bravo et al., 2012)
PD	Preclinical study using in vitro and in vivo PD models	Novel probiotic formulation ***SLAB51*** (combination of nine live bacterial strains *Streptococcus thermophilus*, Bifidobacteria (*Bifidobacterium longum, B. breve, B. infantis*), and *Lactobacilli* (*Lactobacillus acidophilus, L. plantarum, L. paracasei, L.*	Significantly improved the behavioural symptoms and prevented the loss of dopaminergic neurons of substantia nigra and striatum	(Liu et al., 2019)

		delbrueckii subsp. *bulgaricus, L. brevis*) adminstration		
PD	In vitro study	Probiotics *L. salivarius* (LS_{01}) *and L. acidophilus* (LA_{02})	significantly decreased the levels of proinflammatory cytokines and ROS, and increased the anti-inflammatory cytokines in peripheral blood mononuclear cells of PD patients	(Magistrelli et al., 2019)
PD	A randomized, double-blind, placebo-controlled study	Consumption of fermented milk with multiple probiotic strains and prebiotic fibres	Significantly alleviated constipation in PD patients	(Barichella et al., 2016)
PD	A clinical study	Consumption of fermented milk containing *L. casei Shirota*	Notably improved the stool consistency as well as decreased bloating and abdominal pain	(Cassani et al., 2011)
PD	A randomized, double-blind, controlled trial	Administration of probiotics containing *Bifidobacteria* and *Lactobacilli* (B/L) species (*L.*	Significantly improved the motor scores and some metabolic profiles in PD patients	(Tamtaji et al., 2019b)

		acidophilus, L. reuteri, L. fermentum, and B. bifidum)		
AD	Animal models with AD induced by intracerebroventricular injection of Aβ (1-42) in rats or by intraperitoneal injection of D-Galactose (120 mg/kg body) into albino rats.	Oral delivery of probiotic B/L mixtures	Significantly enhanced the learning and memory, decreased the level of OS and pathological cellular changes in the brain and proteolytic functions	(Athari Nik Azm et al., 2018; Bonfili et al., 2017; Nimgampalle and Kuna, 2017; Rezaei Asl et al., 2019)
AD	An in vivo study in rats with Aβ-induced AD	Probiotics (*L. acidophilus, B. bifidum, and B. longum*) treatment for 4 weeks	Significantly improved spatial learning and memory, long-term potentiation, paired-pulse facilitation ratios, and lipid profiles	(Kobayashi et al., 2018; Rezaei Asl et al., 2019)

AD	A transgenic study using APP/PS1 mice	Treatment with *Akkermansia muciniphila*	Reduced the levels of fasting blood glucose, lipids and serum diamine oxidase and cerebral Aβ 40–42	(Ou et al., 2020)
AD	A transgenic study using a 3xTg AD mouse model	Oral administration of *SLAB51* for 4 months	Significant reduction in impairment, Aβ aggregation, and alternation of neuronal proteolysis along with a promising reduction of pro-inflammatory cytokines and increase in anti-inflammatory cytokines, via the activation of SIRT1 pathway	(Bonfili et al., 2017)
AD	A study in a rat model of AD	Oral administration of probiotics (L. reuteri, L. rhamnosus, and B. infantis)	Significantly improved spatial memory and decreased Aβ plaques, oxidative (malondialdehyde), and	(Mehrabadi and Sadr, 2020)

			inflammatory (IL-1β and TNF-α) markers	
AD	A transgenic study using a humanized Drosophila model of AD	Treatment with a novel synbiotic (Triphala and L. plantarum, L. fermentum, and B. longum subsp. infantis)	Increased the motility and survivability, and decreased Aβ accumulation and acetylcholinesterase activity	(Westfall et al., 2019)
AD	A transgenic study in APP/PS1 mouse model of AD	Butyrate treatment	Improved memory function and increases expression of genes implicated in associative learning	(Govindarajan et al., 2011)
Aging	Animal study using aged rats	Administration of probiotic mixture VSL#3 (combination of *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. longum*,	Provided positive effects on the inflammatory and neuronal processes in the brain cortex of aged rats,	(Distrutti et al., 2014)

		B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, and L. delbrueckii subspecies Bulgaricus)	suggesting an improvement in memory	
AD	Small-scale human studies	Probiotic B/L mixtures	Improved the cognitive and metabolic functions as well as decrease the inflammatory markers in AD patients	(Kobayashi et al., 2019; Leblhuber et al., 2018)
AD	A randomized, double-blinded, placebo-controlled clinical trial	Oral consumption of probiotic B/L mixture for 12 weeks	Significant improvement in cognitive functions along with reduction in high sensitivity CRP, insulin, serum triglycerides, very low-density lipoproteins, and low-density lipoproteins levels and significant increase in total antioxidant capacity were noted in AD patients compared	(Tamtaji et al., 2019a)

			with those treated with only selenium and placebo	
AD	A recent double-blind, randomized, placebo-controlled trial	Synbiotic supplementation containing L. acidophilus, L. casei, B. bifidum and L. fermentum for 12 weeks	Better improvement in learning and memory as well as β-cell function along with reduction in CRP, malondialdehyde, insulin resistance and serum triglycerides were seen in 30 AD patients vs. no treatment in disease-matched control subjects.	(Ton et al., 2020)
MS	A clinical study	Daily intake of probiotic (L. paracasei, L. plantarum, L. acidophilus, L. delbrueckii, B. longum, B. infantis, B. breve, and Streptococcus thermophilus) for 2 months	Significantly improved MS symptoms by modulation of gut microbiota and anti-inflammatory peripheral immune response in MS patients	(Tankou et al., 2018b)

MS	An in vivo study using female SJL/J mice subcutaneously injected with MBP_{83-99} mannan peptide conjugate (50 μg/mouse)	Probiotic treatment with S. thermophilus ST285	Significantly reduced proinflammatory (IL-1β and IFN-γ) and anti-inflammatory (IL-4, IL-5, and IL-10) cytokines in mice immunized with MS peptide	(Dargahi et al., 2020)
MS	A clinical study	Prebiotic treatment with glatiramer acetate	Increased the relative abundance of *Clostridiales*, *Bacteroidaceae*, *Faecalibacterium, Ruminococcus,* *Lactobacillaceae*, *Clostridium*, and other members of the class *Clostridiales* when compared with untreated MS patients.	(Adamczyk-Sowa et al., 2017)
ALS	A prospective longitudinal study	Probiotics supplementation for 6 months	Restores the healthy gut bacterial composition, especially *Rikenellaceae*	(Di Gioia et al., 2020)

			family in ALS patients compared to control group	
Autism	A study using mouse model of ASD	B. fragilis	Significantly improved stereotyped and anxiety-related behaviours as well as the intestinal permeability in the maternal immune mouse model of autism	(Hsiao et al., 2013)
Chronic psychosocial stress	Healthy rats	Prebiotic mixture of fructo-oligosaccharides and GOS	Significantly improved depression and anxiety-related behaviour in mice subjected to chronic psychosocial stress as well as increased the levels of hippocampal BDNF in healthy rats	(Burokas et al., 2017; Savignac et al., 2013)
PD	A clinical study	Supplementation with prebiotic fibres	Improved the compromised gut motility and immune function in PD patients	(Cantu-Jungles et al., 2019)

Mouse model with *Atg5*-deficient intestinal epithelia (mimicking defective autophagy)	An experimental study using intestinal epithelium-specific *Atg5* knockout mouse model	Prebiotic Bimuno-GOS treatment	Alleviated cognitive functions and significantly reduced microglia activation as well as the expression of iNOS, CD68, CD32, SOCS3, and IL-6 in *Atg5* -deficient mice	(Yang et al., 2018)
ASD	Open-label clinical studies	FMT from healthy donors to ASD children	Significantly improved the GI and ASD symptoms in autistic children	(Kang et al., 2019; Zhao et al., 2019)
AD with severe gut dysbiosis	A transgenic study using PAP mice	FMT from healthy WT to PAP mice	Significantly improved synaptic and cognitive functions as well as reduced Aβ accumulation and microglia-mediated neuroinflammation, mainly	(Barichella et al., 2016; Fasano et al., 2013)

			mediated by attaining eubiosis and restoring SCFAs production	
AD	A study of FMT in AD animal model	Both frequent and long-term FMT from healthy WT mice into $ADLP^{APT}$ mice	Alleviated Aβ deposition, tau pathology, glial reactivity and cognitive impairment. Specifically, long-term transfer of healthy faecal microbiota to $ADLP^{APT}$ mice reversed abnormalities in the colonic expression of genes related to intestinal macrophage activity and the circulating blood inflammatory monocytes, similar to those seen in WT mice.	(Kim et al., 2020)
MS	Clinical studies and randomized controlled trials	FMT from healthy donors to MS patients	Improved the motor symptoms and halted the disease progression in MS patients	(Borody and Khoruts, 2011;

				Makkawi et al., 2018)
PD	A case study	FMT from healthy young donors to a 71-year-old PD patient	improvement in tremors and GI symptoms were reported	(Huang et al., 2019)

6.3. Antibiotics

A clinical study showed that antibiotic treatment improves GI symptoms and motor defects in PD patients (Fasano et al., 2013). Phase II trials have confirmed the neuroprotective effects of minocycline on nigrostriatal dopaminergic neurons by targeting TLR4 receptors in PD patients, by reducing F/B ratio (restoring the eubiosis) (Parashar and Udayabanu, 2017) **(Table 2)**.

6.4. Faecal microbiota transplantation (FMT)

FMT is the delivery of faecal material containing gut microbiota from a healthy donor to a recipient with a dysbiosis-related condition, via enema, nasogastric, nasoenteric or endoscopic routes, to restore normal diversity of the microbial community (Staley et al., 2017). FMT has emerged as a promising strategy to restore gut dysbiosis involved in NDDs (Bakken, 2009; Borody and Khoruts, 2011). A previous study showed that FMT modulates brain function and behaviour of the host mice (Bercik et al., 2011), while a recent study in GF mice that received FMT from patients with major depressive disorder confirmed the development of depression-like behaviour (C. Zhang et al., 2017). Furthermore, microbiota-depleted rats that received FMT from depressed patients develop depressive-like symptoms (Kelly et al., 2016), and a dysregulation in tryptophan metabolism, similar to clinical cases reported in autism, schizophrenia and NDDs (McFarlane et al., 2008) **(Table 2)**.

7. Conclusion

The gut microbiota plays a crucial role in the neuropathogenesis of CNS-related disorders by altering GBA function either directly or indirectly. Gut dysbiosis due to an increased burden of pathogenic microbes and metabolites compromises the integrity of the gut barrier and BBB, promoting the migration and infiltration of immunoregulatory cells to the brain, which induces neuroinflammation by affecting the functions of microglia and Treg cells. A vicious cycle

characterized by gut dysbiosis-induced immune dysfunction, deposition and spreading of misfolded proteins, and chronic inflammation triggers the seeding and propagation of misfolded proteins to adjacent healthy neurons. Although there is a growing body of evidence which demonstrates a link between gut dysbiosis and proteinopathies, further studies are required to understand how spreading of misfolded proteins from the periphery to the CNS and neuronal autophagy is implicated in NDDs. Therapeutic interventions aimed at eubiosis by correcting dysfunctional immune responses and autophagy can prevent or slow down the progression of proteinopathies in the NDDs. Modulation of dysbiotic state by nutritional interventions or probiotics, prebiotics, synbiotics and antibiotics may become novel therapeutic strategies to restrain the pathogenesis of CNS-related diseases and cognitive impairment seen with age. Further mechanistic studies in well-defined animal models of NDD will help elucidate how best to modulate GBA function using microbiome-based therapies. Future directions using well-controlled human clinical trials are urgently needed to substantiate the clinical use of probiotics, prebiotics, synbiotics and FMT in NDDs.

8. Declarations

- **Conflict of Interest Statement :** All other authors express no conflict of interest.
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References:

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K.R., Ffytche, D.H., Weintraub, D., Ballard, C., 2017. Cognitive decline in Parkinson disease. Nat. Rev. Neurol. 13, 217–231. https://doi.org/10.1038/nrneurol.2017.27

Abildgaard, A., Elfving, B., Hokland, M., Wegener, G., Lund, S., 2017. Probiotic treatment reduces depressive-like behaviour in rats independently of diet. Psychoneuroendocrinology 79, 40–48. https://doi.org/10.1016/j.psyneuen.2017.02.014

Adamczyk-Sowa, M., Medrek, A., Madej, P., Michlicka, W., Dobrakowski, P., 2017. Does the Gut Microbiota Influence Immunity and Inflammation in Multiple Sclerosis Pathophysiology? J. Immunol. Res. 2017, 7904821. https://doi.org/10.1155/2017/7904821

Afshordel, S., Hagl, S., Werner, D., Röhner, N., Kögel, D., Bazan, N.G., Eckert, G.P., 2015. Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging--impact of Bcl-2 and NPD-1 like metabolites. Prostaglandins Leukot. Essent. Fatty Acids 92, 23–31. https://doi.org/10.1016/j.plefa.2014.05.008

Agus, A., Planchais, J., Sokol, H., 2018. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. Cell Host Microbe 23, 716–724. https://doi.org/10.1016/j.chom.2018.05.003

Ahluwalia, V., Betrapally, N.S., Hylemon, P.B., White, M.B., Gillevet, P.M., Unser, A.B., Fagan, A., Daita, K., Heuman, D.M., Zhou, H., Sikaroodi, M., Bajaj, J.S., 2016. Impaired Gut-Liver-Brain Axis in Patients with Cirrhosis. Sci. Rep. 6, 26800. https://doi.org/10.1038/srep26800

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O.R., Hamidi, G.A., Salami, M., 2016. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind

and Controlled Trial. Front. Aging Neurosci. 8, 256. https://doi.org/10.3389/fnagi.2016.00256

Alam, R., Abdolmaleky, H.M., Zhou, J.-R., 2017. Microbiome, inflammation, epigenetic alterations, and mental diseases. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 174, 651–660. https://doi.org/10.1002/ajmg.b.32567

Amor, S., Puentes, F., Baker, D., van der Valk, P., 2010. Inflammation in neurodegenerative diseases. Immunology 129, 154–169. https://doi.org/10.1111/j.1365-2567.2009.03225.x

Amor, S., Woodroofe, M.N., 2014. Innate and adaptive immune responses in neurodegeneration and repair. Immunology 141, 287–291. https://doi.org/10.1111/imm.12134

Andreasson, K.I., Bachstetter, A.D., Colonna, M., Ginhoux, F., Holmes, C., Lamb, B., Landreth, G., Lee, D.C., Low, D., Lynch, M.A., Monsonego, A., O'Banion, M.K., Pekny, M., Puschmann, T., Russek-Blum, N., Sandusky, L.A., Selenica, M.-L.B., Takata, K., Teeling, J., Town, T., Van Eldik, L.J., Russek-Blum, N., Monsonego, A., Low, D., Takata, K., Ginhoux, F., Town, T., O'Banion, M.K., Lamb, B., Colonna, M., Landreth, G., Andreasson, K.I., Sandusky, L.A., Selenica, M.-L.B., Lee, D.C., Holmes, C., Teeling, J., Lynch, M.A., Van Eldik, L.J., Bachstetter, A.D., Pekny, M., Puschmann, T., 2016. Targeting innate immunity for neurodegenerative disorders of the central nervous system. J. Neurochem. 138, 653–693. https://doi.org/10.1111/jnc.13667

Andrich, J.E., Wobben, M., Klotz, P., Goetze, O., Saft, C., 2009. Upper gastrointestinal findings in Huntington's disease: patients suffer but do not complain. J. Neural Transm. Vienna Austria 1996 116, 1607–1611. https://doi.org/10.1007/s00702-009-0310-1

Arentsen, T., Qian, Y., Gkotzis, S., Femenia, T., Wang, T., Udekwu, K., Forssberg, H., Diaz Heijtz, R., 2017. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates

brain development and behavior. Mol. Psychiatry 22, 257–266. https://doi.org/10.1038/mp.2016.182

Arpaia, N., Campbell, C., Fan, X., Dikiy, S., van der Veeken, J., deRoos, P., Liu, H., Cross, J.R., Pfeffer, K., Coffer, P.J., Rudensky, A.Y., 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 504, 451–455. https://doi.org/10.1038/nature12726

Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., Fernandes, G.R., Tap, J., Bruls, T., Batto, J.-M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., Kurokawa, K., Leclerc, M., Levenez, F., Manichanh, C., Nielsen, H.B., Nielsen, T., Pons, N., Poulain, J., Qin, J., Sicheritz-Ponten, T., Tims, S., Torrents, D., Ugarte, E., Zoetendal, E.G., Wang, J., Guarner, F., Pedersen, O., de Vos, W.M., Brunak, S., Doré, J., Weissenbach, J., Ehrlich, S.D., Bork, P., 2011. Enterotypes of the human gut microbiome. Nature 473, 174–180. https://doi.org/10.1038/nature09944

Atarashi, K., Tanoue, T., Shima, T., Imaoka, A., Kuwahara, T., Momose, Y., Cheng, G., Yamasaki, S., Saito, T., Ohba, Y., Taniguchi, T., Takeda, K., Hori, S., Ivanov, I.I., Umesaki, Y., Itoh, K., Honda, K., 2011. Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331, 337–341. https://doi.org/10.1126/science.1198469

Athari Nik Azm, S., Djazayeri, A., Safa, M., Azami, K., Ahmadvand, B., Sabbaghziarani, F., Sharifzadeh, M., Vafa, M., 2018. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β-amyloid (1-42) injected rats. Appl. Physiol. Nutr. Metab. Physiol. Appl. Nutr. Metab. 43, 718–726. https://doi.org/10.1139/apnm-2017-0648

Azad, M.A.K., Sarker, M., Li, T., Yin, J., 2018. Probiotic Species in the Modulation of Gut Microbiota: An Overview. BioMed Res. Int. 2018, 9478630. https://doi.org/10.1155/2018/9478630

Bäckhed, F., 2011. Programming of host metabolism by the gut microbiota. Ann. Nutr. Metab. 58 Suppl 2, 44–52. https://doi.org/10.1159/000328042

Bakken, J.S., 2009. Fecal bacteriotherapy for recurrent Clostridium difficile infection. Anaerobe 15, 285–289. https://doi.org/10.1016/j.anaerobe.2009.09.007

Ballway, J.W., Song, B.-J., 2021. Translational Approaches with Antioxidant Phytochemicals against Alcohol-Mediated Oxidative Stress, Gut Dysbiosis, Intestinal Barrier Dysfunction, and Fatty Liver Disease. Antioxid. Basel Switz. 10. https://doi.org/10.3390/antiox10030384

Baquero, F., Nombela, C., 2012. The microbiome as a human organ. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 18 Suppl 4, 2–4. https://doi.org/10.1111/j.1469-0691.2012.03916.x

Barichella, M., Pacchetti, C., Bolliri, C., Cassani, E., Iorio, L., Pusani, C., Pinelli, G., Privitera, G., Cesari, I., Faierman, S.A., Caccialanza, R., Pezzoli, G., Cereda, E., 2016. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. Neurology 87, 1274–1280. https://doi.org/10.1212/WNL.0000000000003127

Barichella, M., Severgnini, M., Cilia, R., Cassani, E., Bolliri, C., Caronni, S., Ferri, V., Cancello, R., Ceccarani, C., Faierman, S., Pinelli, G., De Bellis, G., Zecca, L., Cereda, E., Consolandi, C., Pezzoli, G., 2019. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. Mov. Disord. Off. J. Mov. Disord. Soc. 34, 396–405. https://doi.org/10.1002/mds.27581

Baruch, K., Rosenzweig, N., Kertser, A., Deczkowska, A., Sharif, A.M., Spinrad, A., Tsitsou-Kampeli, A., Sarel, A., Cahalon, L., Schwartz, M., 2015. Breaking immune tolerance

by targeting Foxp3(+) regulatory T cells mitigates Alzheimer's disease pathology. Nat. Commun. 6, 7967. https://doi.org/10.1038/ncomms8967

Basavarajappa, B.S., Subbanna, S., 2021. Histone Methylation Regulation in Neurodegenerative Disorders. Int. J. Mol. Sci. 22, 4654. https://doi.org/10.3390/ijms22094654

Bauer, K.C., Huus, K.E., Finlay, B.B., 2016. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. Cell. Microbiol. 18, 632–644. https://doi.org/10.1111/cmi.12585

Bauer, K.C., Rees, T., Finlay, B.B., 2019. The Gut Microbiota–Brain Axis Expands Neurologic Function: A Nervous Rapport. BioEssays 41, 1800268. https://doi.org/10.1002/bies.201800268

Bayer, T.A., 2015. Proteinopathies, a core concept for understanding and ultimately treating degenerative disorders? Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 713–724. https://doi.org/10.1016/j.euroneuro.2013.03.007

Beamer, C.A., Shepherd, D.M., 2012. Inhibition of TLR ligand- and interferon gamma-induced murine microglial activation by Panax notoginseng. J. Neuroimmune Pharmacol. Off. J. Soc. NeuroImmune Pharmacol. 7, 465–476. https://doi.org/10.1007/s11481-011-9333-0

Bellono, N.W., Bayrer, J.R., Leitch, D.B., Castro, J., Zhang, C., O'Donnell, T.A., Brierley, S.M., Ingraham, H.A., Julius, D., 2017. Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways. Cell 170, 185-198.e16. https://doi.org/10.1016/j.cell.2017.05.034

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., Macri, J., McCoy, K.D., Verdu, E.F., Collins, S.M., 2011. The intestinal microbiota

affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology 141, 599–609, 609.e1–3. https://doi.org/10.1053/j.gastro.2011.04.052

Berer, K., Gerdes, L.A., Cekanaviciute, E., Jia, X., Xiao, L., Xia, Z., Liu, C., Klotz, L., Stauffer, U., Baranzini, S.E., Kümpfel, T., Hohlfeld, R., Krishnamoorthy, G., Wekerle, H., 2017. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc. Natl. Acad. Sci. U. S. A. 114, 10719–10724. https://doi.org/10.1073/pnas.1711233114

Berer, K., Mues, M., Koutrolos, M., Rasbi, Z.A., Boziki, M., Johner, C., Wekerle, H., Krishnamoorthy, G., 2011. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature 479, 538–541. https://doi.org/10.1038/nature10554

Bhargava, P., Mowry, E.M., 2014. Gut microbiome and multiple sclerosis. Curr. Neurol. Neurosci. Rep. 14, 492. https://doi.org/10.1007/s11910-014-0492-2

Biasucci, G., Rubini, M., Riboni, S., Morelli, L., Bessi, E., Retetangos, C., 2010. Mode of delivery affects the bacterial community in the newborn gut. Early Hum. Dev. 86 Suppl 1, 13–15. https://doi.org/10.1016/j.earlhumdev.2010.01.004

Bishir, M., Bhat, A., Essa, M.M., Ekpo, O., Ihunwo, A.O., Veeraraghavan, V.P., Mohan, S.K., Mahalakshmi, A.M., Ray, B., Tuladhar, S., Chang, S., Chidambaram, S.B., Sakharkar, M.K., Guillemin, G.J., Qoronfleh, M.W., Ojcius, D.J., 2020. Sleep Deprivation and Neurological Disorders [WWW Document]. BioMed Res. Int. https://doi.org/10.1155/2020/5764017

Bjarnason, Ingvar T., Bjarnason, Inguar T., Charlett, A., Dobbs, R.J., Dobbs, S.M., Ibrahim, M.A.A., Kerwin, R.W., Mahler, R.F., Oxlade, N.L., Peterson, D.W., Plant, J.M., Price, A.B., Weller, C., 2005. Role of chronic infection and inflammation in the

gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 2: response of facets of clinical idiopathic parkinsonism to Helicobacter pylori eradication. A randomized, double-blind, placebo-controlled efficacy study. Helicobacter 10, 276–287. https://doi.org/10.1111/j.1523-5378.2005.00330.x

Blacher, E., Bashiardes, S., Shapiro, H., Rothschild, D., Mor, U., Dori-Bachash, M., Kleimeyer, C., Moresi, C., Harnik, Y., Zur, M., Zabari, M., Brik, R.B.-Z., Kviatcovsky, D., Zmora, N., Cohen, Y., Bar, N., Levi, I., Amar, N., Mehlman, T., Brandis, A., Biton, I., Kuperman, Y., Tsoory, M., Alfahel, L., Harmelin, A., Schwartz, M., Israelson, A., Arike, L., Johansson, M.E.V., Hansson, G.C., Gotkine, M., Segal, E., Elinav, E., 2019. Potential roles of gut microbiome and metabolites in modulating ALS in mice. Nature 572, 474–480. https://doi.org/10.1038/s41586-019-1443-5

Bohórquez, D.V., Shahid, R.A., Erdmann, A., Kreger, A.M., Wang, Y., Calakos, N., Wang, F., Liddle, R.A., 2015. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J. Clin. Invest. 125, 782–786. https://doi.org/10.1172/JCI78361

Bolognini, D., Tobin, A.B., Milligan, G., Moss, C.E., 2016. The Pharmacology and Function of Receptors for Short-Chain Fatty Acids. Mol. Pharmacol. 89, 388–398. https://doi.org/10.1124/mol.115.102301

Bonfili, L., Cecarini, V., Berardi, S., Scarpona, S., Suchodolski, J.S., Nasuti, C., Fiorini, D., Boarelli, M.C., Rossi, G., Eleuteri, A.M., 2017. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci. Rep. 7, 2426. https://doi.org/10.1038/s41598-017-02587-2

Borody, T.J., Khoruts, A., 2011. Fecal microbiota transplantation and emerging applications. Nat. Rev. Gastroenterol. Hepatol. 9, 88–96. https://doi.org/10.1038/nrgastro.2011.244

Borre, Y.E., O'Keeffe, G.W., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2014. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol. Med. 20, 509–518. https://doi.org/10.1016/j.molmed.2014.05.002

Bostancikliоğlu, M., 2018. Intestinal Bacterial Flora and Alzheimer's Disease. Neurophysiology 50, 140–148. https://doi.org/10.1007/s11062-018-9728-0

Boya, P., Reggiori, F., Codogno, P., 2013. Emerging regulation and functions of autophagy. Nat. Cell Biol. 15, 713–720. https://doi.org/10.1038/ncb2788

Braak, H., Del Tredici, K., 2008. [A new look at the corticostriatal-thalamocortical circuit in sporadic Parkinson's disease]. Nervenarzt 79, 1440–1445. https://doi.org/10.1007/s00115-008-2542-y

Braak, Heiko, Del Tredici, K., 2008. Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. Exp. Neurol. 212, 226–229. https://doi.org/10.1016/j.expneurol.2008.04.001

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., Del Tredici, K., 2004. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 318, 121–134. https://doi.org/10.1007/s00441-004-0956-9

Brandscheid, C., Schuck, F., Reinhardt, S., Schäfer, K.-H., Pietrzik, C.U., Grimm, M., Hartmann, T., Schwiertz, A., Endres, K., 2017. Altered Gut Microbiome Composition and Tryptic Activity of the 5xFAD Alzheimer's Mouse Model. J. Alzheimers Dis. JAD 56, 775–788. https://doi.org/10.3233/JAD-160926

Bravo, J.A., Julio-Pieper, M., Forsythe, P., Kunze, W., Dinan, T.G., Bienenstock, J., Cryan, J.F., 2012. Communication between gastrointestinal bacteria and the nervous system. Curr. Opin. Pharmacol. 12, 667–672. https://doi.org/10.1016/j.coph.2012.09.010

Brenner, S.R., 2013. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be

related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. Med. Hypotheses 80, 103. https://doi.org/10.1016/j.mehy.2012.10.010

Brown, R.H., Al-Chalabi, A., 2017. Amyotrophic Lateral Sclerosis. N. Engl. J. Med. 377, 162–172. https://doi.org/10.1056/NEJMra1603471

Browning, K.N., Travagli, R.A., 2014. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr. Physiol. 4, 1339–1368. https://doi.org/10.1002/cphy.c130055

Brundin, P., Melki, R., Kopito, R., 2010. Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat. Rev. Mol. Cell Biol. 11, 301–307. https://doi.org/10.1038/nrm2873

Burokas, A., Arboleya, S., Moloney, R.D., Peterson, V.L., Murphy, K., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2017. Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. Biol. Psychiatry 82, 472–487. https://doi.org/10.1016/j.biopsych.2016.12.031

C, P., L, A., V, C., R, C., M, F., C, B., 2020. Microbiota-gut-brain axis in health and disease: Is NLRP3 inflammasome at the crossroads of microbiota-gut-brain communications? [WWW Document]. Prog. Neurobiol. https://doi.org/10.1016/j.pneurobio.2020.101806

Cabrera-Pastor, A., Llansola, M., Montoliu, C., Malaguarnera, M., Balzano, T., Taoro-Gonzalez, L., García-García, R., Mangas-Losada, A., Izquierdo-Altarejos, P., Arenas, Y.M., Leone, P., Felipo, V., 2019. Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic

encephalopathy: Underlying mechanisms and therapeutic implications. Acta Physiol. Oxf. Engl. 226, e13270. https://doi.org/10.1111/apha.13270

Calvani, R., Picca, A., Lo Monaco, M.R., Landi, F., Bernabei, R., Marzetti, E., 2018. Of Microbes and Minds: A Narrative Review on the Second Brain Aging. Front. Med. 5. https://doi.org/10.3389/fmed.2018.00053

Cantu-Jungles, T.M., Rasmussen, H.E., Hamaker, B.R., 2019. Potential of Prebiotic Butyrogenic Fibers in Parkinson's Disease. Front. Neurol. 10, 663. https://doi.org/10.3389/fneur.2019.00663

Caputi, V., Giron, M.C., 2018. Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson's Disease. Int. J. Mol. Sci. 19. https://doi.org/10.3390/ijms19061689

Carabotti, M., Scirocco, A., Maselli, M.A., Severi, C., 2015. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann. Gastroenterol. Q. Publ. Hell. Soc. Gastroenterol. 28, 203–209.

Cassani, E., Privitera, G., Pezzoli, G., Pusani, C., Madio, C., Iorio, L., Barichella, M., 2011. Use of probiotics for the treatment of constipation in Parkinson's disease patients. Minerva Gastroenterol. Dietol. 57, 117–121.

Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., Ferrari, C., Guerra, U.P., Paghera, B., Muscio, C., Bianchetti, A., Volta, G.D., Turla, M., Cotelli, M.S., Gennuso, M., Prelle, A., Zanetti, O., Lussignoli, G., Mirabile, D., Bellandi, D., Gentile, S., Belotti, G., Villani, D., Harach, T., Bolmont, T., Padovani, A., Boccardi, M., Frisoni, G.B., INDIA-FBP Group, 2017. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol. Aging 49, 60–68. https://doi.org/10.1016/j.neurobiolaging.2016.08.019

Cekanaviciute, E., Debelius, J.W., Singh, S., Runia, T., Nelson, C., Yoo, B., Kanner, R., Crabtree-Hartman, E., Mazmanian, S., Knight, R., Katz Sand, I., Casaccia, P., Cree, B.A.C., Baranzini, S.E., 2016. Gut dysbiosis is a feature of MS and it is characterized by bacteria able to regulate lymphocyte differentiation in vitro. Mult. Scler. J. 22, 58–59.

Cekanaviciute, E., Yoo, B.B., Runia, T.F., Debelius, J.W., Singh, S., Nelson, C.A., Kanner, R., Bencosme, Y., Lee, Y.K., Hauser, S.L., Crabtree-Hartman, E., Sand, I.K., Gacias, M., Zhu, Y., Casaccia, P., Cree, B.A.C., Knight, R., Mazmanian, S.K., Baranzini, S.E., 2017. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proc. Natl. Acad. Sci. U. S. A. 114, 10713–10718. https://doi.org/10.1073/pnas.1711235114

Chandra, R., Hiniker, A., Kuo, Y.-M., Nussbaum, R.L., Liddle, R.A., 2017. α-Synuclein in gut endocrine cells and its implications for Parkinson's disease. JCI Insight 2. https://doi.org/10.1172/jci.insight.92295

Chauhan, S., Mandell, M.A., Deretic, V., 2015. IRGM governs the core autophagy machinery to conduct antimicrobial defense. Mol. Cell 58, 507–521. https://doi.org/10.1016/j.molcel.2015.03.020

Chen, J., Chia, N., Kalari, K.R., Yao, J.Z., Novotna, M., Paz Soldan, M.M., Luckey, D.H., Marietta, E.V., Jeraldo, P.R., Chen, X., Weinshenker, B.G., Rodriguez, M., Kantarci, O.H., Nelson, H., Murray, J.A., Mangalam, A.K., 2016. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci. Rep. 6, 28484. https://doi.org/10.1038/srep28484

Chen, S.G., Stribinskis, V., Rane, M.J., Demuth, D.R., Gozal, E., Roberts, A.M., Jagadapillai, R., Liu, R., Choe, K., Shivakumar, B., Son, F., Jin, S., Kerber, R., Adame, A., Masliah, E., Friedland, R.P., 2016. Exposure to the Functional Bacterial Amyloid Protein Curli

Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and Caenorhabditis elegans. Sci. Rep. 6, 34477. https://doi.org/10.1038/srep34477

Chen, T., Noto, D., Hoshino, Y., Mizuno, M., Miyake, S., 2019. Butyrate suppresses demyelination and enhances remyelination. J. Neuroinflammation 16, 165. https://doi.org/10.1186/s12974-019-1552-y

Chevalier, A.C., Rosenberger, T.A., 2017. Increasing acetyl-CoA metabolism attenuates injury and alters spinal cord lipid content in mice subjected to experimental autoimmune encephalomyelitis. J. Neurochem. 141, 721–737. https://doi.org/10.1111/jnc.14032

Chia, S., Flagmeier, P., Habchi, J., Lattanzi, V., Linse, S., Dobson, C.M., Knowles, T.P.J., Vendruscolo, M., 2017. Monomeric and fibrillar α-synuclein exert opposite effects on the catalytic cycle that promotes the proliferation of Aβ42 aggregates. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1700239114

Chiti, F., Dobson, C.M., 2017. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu. Rev. Biochem. 86, 27–68. https://doi.org/10.1146/annurev-biochem-061516-045115

Chitnis, T., Weiner, H.L., 2017. CNS inflammation and neurodegeneration. J. Clin. Invest. 127, 3577–3587. https://doi.org/10.1172/JCI90609

Cho, Y.-E., Kim, D.-K., Seo, W., Gao, B., Yoo, S.-H., Song, B.-J., 2019. Fructose Promotes Leaky Gut, Endotoxemia, and Liver Fibrosis Through Ethanol-Inducible Cytochrome P450-2E1-Mediated Oxidative and Nitrative Stress. Hepatol. Baltim. Md. https://doi.org/10.1002/hep.30652

Ciccocioppo, F., Lanuti, P., Pierdomenico, L., Simeone, P., Bologna, G., Ercolino, E., Buttari, F., Fantozzi, R., Thomas, A., Onofrj, M., Centonze, D., Miscia, S., Marchisio, M., 2019. The Characterization of Regulatory T-Cell Profiles in Alzheimer's Disease and Multiple Sclerosis. Sci. Rep. 9, 8788. https://doi.org/10.1038/s41598-019-45433-3

Clarke, G., Stilling, R.M., Kennedy, P.J., Stanton, C., Cryan, J.F., Dinan, T.G., 2014. Minireview: Gut microbiota: the neglected endocrine organ. Mol. Endocrinol. Baltim. Md 28, 1221–1238. https://doi.org/10.1210/me.2014-1108

Coccia, M., Harrison, O.J., Schiering, C., Asquith, M.J., Becher, B., Powrie, F., Maloy, K.J., 2012. IL-1β mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. J. Exp. Med. 209, 1595–1609. https://doi.org/10.1084/jem.20111453

Collins, S.M., Bercik, P., 2009. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology 136, 2003–2014. https://doi.org/10.1053/j.gastro.2009.01.075

Collins, S.M., Surette, M., Bercik, P., 2012. The interplay between the intestinal microbiota and the brain. Nat. Rev. Microbiol. 10, 735–742. https://doi.org/10.1038/nrmicro2876

Coman, V., Vodnar, D.C., 2020. Gut microbiota and old age: Modulating factors and interventions for healthy longevity. Exp. Gerontol. 141, 111095. https://doi.org/10.1016/j.exger.2020.111095

Coulombe, K., Kerdiles, O., Tremblay, C., Emond, V., Lebel, M., Boulianne, A.-S., Plourde, M., Cicchetti, F., Calon, F., 2018. Impact of DHA intake in a mouse model of synucleinopathy. Exp. Neurol. 301, 39–49. https://doi.org/10.1016/j.expneurol.2017.12.002

Cruciani, G., Valeri, A., Goracci, L., Pellegrino, R.M., Buonerba, F., Baroni, M., 2014. Flavin monooxygenase metabolism: why medicinal chemists should matter. J. Med. Chem. 57, 6183–6196. https://doi.org/10.1021/jm5007098

Crumeyrolle-Arias, M., Jaglin, M., Bruneau, A., Vancassel, S., Cardona, A., Daugé, V., Naudon, L., Rabot, S., 2014. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats.

Psychoneuroendocrinology 42, 207–217. https://doi.org/10.1016/j.psyneuen.2014.01.014

Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13, 701–712. https://doi.org/10.1038/nrn3346

Dąbek, A., Wojtala, M., Pirola, L., Balcerczyk, A., 2020. Modulation of Cellular Biochemistry, Epigenetics and Metabolomics by Ketone Bodies. Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States. Nutrients 12, 788. https://doi.org/10.3390/nu12030788

Dalile, B., Van Oudenhove, L., Vervliet, B., Verbeke, K., 2019. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat. Rev. Gastroenterol. Hepatol. 16, 461–478. https://doi.org/10.1038/s41575-019-0157-3

Danese, A., Baldwin, J.R., 2017. Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. Annu. Rev. Psychol. 68, 517–544. https://doi.org/10.1146/annurev-psych-010416-044208

Dansokho, C., Ait Ahmed, D., Aid, S., Toly-Ndour, C., Chaigneau, T., Calle, V., Cagnard, N., Holzenberger, M., Piaggio, E., Aucouturier, P., Dorothée, G., 2016. Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain J. Neurol. 139, 1237–1251. https://doi.org/10.1093/brain/awv408

Dargahi, N., Matsoukas, J., Apostolopoulos, V., 2020. Streptococcusthermophilus ST285 Alters Pro-Inflammatory to Anti-Inflammatory Cytokine Secretion against Multiple Sclerosis Peptide in Mice. Brain Sci. 10. https://doi.org/10.3390/brainsci10020126

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., Biddinger, S.B., Dutton, R.J.,

Turnbaugh, P.J., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563. https://doi.org/10.1038/nature12820

De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchampt, A., Bäckhed, F., Mithieux, G., 2014. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156, 84–96. https://doi.org/10.1016/j.cell.2013.12.016

de Vos, W.M., de Vos, E.A.J., 2012. Role of the intestinal microbiome in health and disease: from correlation to causation. Nutr. Rev. 70 Suppl 1, S45-56. https://doi.org/10.1111/j.1753-4887.2012.00505.x

Dehay, B., Martinez-Vicente, M., Caldwell, G.A., Caldwell, K.A., Yue, Z., Cookson, M.R., Klein, C., Vila, M., Bezard, E., 2013. Lysosomal impairment in Parkinson's disease. Mov. Disord. Off. J. Mov. Disord. Soc. 28, 725–732. https://doi.org/10.1002/mds.25462

Del Tredici, K., Hawkes, C.H., Ghebremedhin, E., Braak, H., 2010. Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol. (Berl.) 119, 703–713. https://doi.org/10.1007/s00401-010-0665-2

Deleidi, M., Maetzler, W., 2012. Protein clearance mechanisms of alpha-synuclein and amyloid-Beta in lewy body disorders. Int. J. Alzheimers Dis. 2012, 391438. https://doi.org/10.1155/2012/391438

Den, H., Dong, X., Chen, M., Zou, Z., 2020. Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment - a meta-analysis of randomized controlled trials. Aging 12, 4010–4039. https://doi.org/10.18632/aging.102810

Dendrou, C.A., Fugger, L., Friese, M.A., 2015. Immunopathology of multiple sclerosis. Nat. Rev. Immunol. 15, 545–558. https://doi.org/10.1038/nri3871

Depeint, F., Tzortzis, G., Vulevic, J., I'anson, K., Gibson, G.R., 2008. Prebiotic evaluation of a novel galactooligosaccharide mixture produced by the enzymatic activity of Bifidobacterium bifidum NCIMB 41171, in healthy humans: a randomized, double-blind, crossover, placebo-controlled intervention study. Am. J. Clin. Nutr. 87, 785–791. https://doi.org/10.1093/ajcn/87.3.785

Devos, D., Lebouvier, T., Lardeux, B., Biraud, M., Rouaud, T., Pouclet, H., Coron, E., Bruley des Varannes, S., Naveilhan, P., Nguyen, J.-M., Neunlist, M., Derkinderen, P., 2013. Colonic inflammation in Parkinson's disease. Neurobiol. Dis. 50, 42–48. https://doi.org/10.1016/j.nbd.2012.09.007

Di Gioia, D., Bozzi Cionci, N., Baffoni, L., Amoruso, A., Pane, M., Mogna, L., Gaggìa, F., Lucenti, M.A., Bersano, E., Cantello, R., De Marchi, F., Mazzini, L., 2020. A prospective longitudinal study on the microbiota composition in amyotrophic lateral sclerosis. BMC Med. 18, 153. https://doi.org/10.1186/s12916-020-01607-9

Dinan, T.G., Borre, Y.E., Cryan, J.F., 2014. Genomics of schizophrenia: time to consider the gut microbiome? Mol. Psychiatry 19, 1252–1257. https://doi.org/10.1038/mp.2014.93

Dinan, T.G., Cryan, J.F., 2017. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterol. Clin. North Am. 46, 77–89. https://doi.org/10.1016/j.gtc.2016.09.007

Dinan, T.G., Cryan, J.F., 2015. The impact of gut microbiota on brain and behaviour: implications for psychiatry. Curr. Opin. Clin. Nutr. Metab. Care 18, 552–558. https://doi.org/10.1097/MCO.0000000000000221

Distrutti, E., O'Reilly, J.-A., McDonald, C., Cipriani, S., Renga, B., Lynch, M.A., Fiorucci, S., 2014. Modulation of intestinal microbiota by the probiotic VSL#3 resets brain gene

expression and ameliorates the age-related deficit in LTP. PloS One 9, e106503. https://doi.org/10.1371/journal.pone.0106503

Dominguez-Bello, M.G., Costello, E.K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Knight, R., 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. U. S. A. 107, 11971–11975. https://doi.org/10.1073/pnas.1002601107

Donaldson, G.P., Lee, S.M., Mazmanian, S.K., 2016. Gut biogeography of the bacterial microbiota. Nat. Rev. Microbiol. 14, 20–32. https://doi.org/10.1038/nrmicro3552

Drouin-Ouellet, J., Cicchetti, F., 2012. Inflammation and neurodegeneration: the story "retolled." Trends Pharmacol. Sci. 33, 542–551. https://doi.org/10.1016/j.tips.2012.07.002

Dugger, B.N., Perl, D.P., Carlson, G.A., 2017. Neurodegenerative Disease Transmission and Transgenesis in Mice. Cold Spring Harb. Perspect. Biol. 9. https://doi.org/10.1101/cshperspect.a023549

Elshaer, D., Begun, J., 2017. The role of barrier function, autophagy, and cytokines in maintaining intestinal homeostasis. Semin. Cell Dev. Biol. 61, 51–59. https://doi.org/10.1016/j.semcdb.2016.08.018

Erny, D., Hrabě de Angelis, A.L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W.S., McCoy, K.D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., Prinz, M., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18, 965–977. https://doi.org/10.1038/nn.4030

Esposito, T., Varriale, B., D'Angelo, R., Amato, A., Sidoti, A., 2014. Regulation of flavin-containing mono-oxygenase (Fmo3) gene expression by steroids in mice and humans. Horm. Mol. Biol. Clin. Investig. 20, 99–109. https://doi.org/10.1515/hmbci-2014-0012

Etienne, P., Gauthier, S., Johnson, G., Collier, B., Mendis, T., Dastoor, D., Cole, M., Muller, H.F., 1978. Clinical effects of choline in Alzheimer's disease. Lancet Lond. Engl. 1, 508–509. https://doi.org/10.1016/s0140-6736(78)90180-0

Ezendam, J., de Klerk, A., Gremmer, E.R., van Loveren, H., 2008. Effects of Bifidobacterium animalis administered during lactation on allergic and autoimmune responses in rodents. Clin. Exp. Immunol. 154, 424–431. https://doi.org/10.1111/j.1365-2249.2008.03788.x

Fang, X., Wang, Xin, Yang, S., Meng, F., Wang, Xiaolei, Wei, H., Chen, T., 2016. Evaluation of the Microbial Diversity in Amyotrophic Lateral Sclerosis Using High-Throughput Sequencing. Front. Microbiol. 7, 1479. https://doi.org/10.3389/fmicb.2016.01479

Fasano, A., Bove, F., Gabrielli, M., Petracca, M., Zocco, M.A., Ragazzoni, E., Barbaro, F., Piano, C., Fortuna, S., Tortora, A., Di Giacopo, R., Campanale, M., Gigante, G., Lauritano, E.C., Navarra, P., Marconi, S., Gasbarrini, A., Bentivoglio, A.R., 2013. The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov. Disord. Off. J. Mov. Disord. Soc. 28, 1241–1249. https://doi.org/10.1002/mds.25522

Fattorusso, A., Di Genova, L., Dell'Isola, G.B., Mencaroni, E., Esposito, S., 2019. Autism Spectrum Disorders and the Gut Microbiota. Nutrients 11. https://doi.org/10.3390/nu11030521

Femenía, T., Gómez-Galán, M., Lindskog, M., Magara, S., 2012. Dysfunctional hippocampal activity affects emotion and cognition in mood disorders. Brain Res. 1476, 58–70. https://doi.org/10.1016/j.brainres.2012.03.053

Ferreira, S.T., Lourenco, M.V., Oliveira, M.M., De Felice, F.G., 2015. Soluble amyloid-β oligomers as synaptotoxins leading to cognitive impairment in Alzheimer's disease. Front. Cell. Neurosci. 9, 191. https://doi.org/10.3389/fncel.2015.00191

Filomeni, G., De Zio, D., Cecconi, F., 2015. Oxidative stress and autophagy: the clash between damage and metabolic needs. Cell Death Differ. 22, 377–388. https://doi.org/10.1038/cdd.2014.150

Firth, J., Teasdale, S.B., Allott, K., Siskind, D., Marx, W., Cotter, J., Veronese, N., Schuch, F., Smith, L., Solmi, M., Carvalho, A.F., Vancampfort, D., Berk, M., Stubbs, B., Sarris, J., 2019. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 18, 308–324. https://doi.org/10.1002/wps.20672

Fitzgerald, E., Murphy, S., Martinson, H.A., 2019. Alpha-Synuclein Pathology and the Role of the Microbiota in Parkinson's Disease. Front. Neurosci. 13, 369. https://doi.org/10.3389/fnins.2019.00369

Fontana, L., 2018. Interventions to promote cardiometabolic health and slow cardiovascular ageing. Nat. Rev. Cardiol. 15, 566–577. https://doi.org/10.1038/s41569-018-0026-8

Forsythe, P., Bienenstock, J., Kunze, W.A., 2014. Vagal pathways for microbiome-brain-gut axis communication. Adv. Exp. Med. Biol. 817, 115–133. https://doi.org/10.1007/978-1-4939-0897-4_5

Foster, J.A., McVey Neufeld, K.-A., 2013. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 36, 305–312. https://doi.org/10.1016/j.tins.2013.01.005

Foster, J.A., Rinaman, L., Cryan, J.F., 2017. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol. Stress 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Fouhy, F., Guinane, C.M., Hussey, S., Wall, R., Ryan, C.A., Dempsey, E.M., Murphy, B., Ross, R.P., Fitzgerald, G.F., Stanton, C., Cotter, P.D., 2012. High-Throughput Sequencing Reveals the Incomplete, Short-Term Recovery of Infant Gut Microbiota

following Parenteral Antibiotic Treatment with Ampicillin and Gentamicin. Antimicrob. Agents Chemother. 56, 5811–5820. https://doi.org/10.1128/AAC.00789-12

Fox, M., Knorr, D.A., Haptonstall, K.M., 2019. Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective. Ann. N. Y. Acad. Sci. 1449, 3–24. https://doi.org/10.1111/nyas.14129

Frank, D.N., Amand, A.L.S., Feldman, R.A., Boedeker, E.C., Harpaz, N., Pace, N.R., 2007. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc. Natl. Acad. Sci. 104, 13780–13785. https://doi.org/10.1073/pnas.0706625104

Friedland, R.P., 2015. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. J. Alzheimers Dis. JAD 45, 349–362. https://doi.org/10.3233/JAD-142841

Friedland, R.P., Chapman, M.R., 2017. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 13, e1006654. https://doi.org/10.1371/journal.ppat.1006654

Fu, X., Liu, Z., Zhu, C., Mou, H., Kong, Q., 2019. Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria. Crit. Rev. Food Sci. Nutr. 59, S130–S152. https://doi.org/10.1080/10408398.2018.1542587

Fujii, Y., Nguyen, T.T.T., Fujimura, Y., Kameya, N., Nakamura, S., Arakawa, K., Morita, H., 2019. Fecal metabolite of a gnotobiotic mouse transplanted with gut microbiota from a patient with Alzheimer's disease. Biosci. Biotechnol. Biochem. 83, 2144–2152. https://doi.org/10.1080/09168451.2019.1644149

Fung, T.C., Olson, C.A., Hsiao, E.Y., 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nat. Neurosci. 20, 145–155. https://doi.org/10.1038/nn.4476

Furukawa, Y., Kaneko, K., Matsumoto, G., Kurosawa, M., Nukina, N., 2009. Cross-Seeding Fibrillation of Q/N-Rich Proteins Offers New Pathomechanism of Polyglutamine Diseases. J. Neurosci. 29, 5153–5162. https://doi.org/10.1523/JNEUROSCI.0783-09.2009

Gacias, M., Gaspari, S., Santos, P.-M.G., Tamburini, S., Andrade, M., Zhang, F., Shen, N., Tolstikov, V., Kiebish, M.A., Dupree, J.L., Zachariou, V., Clemente, J.C., Casaccia, P., 2016. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. eLife 5. https://doi.org/10.7554/eLife.13442

Gagliani, N., Palm, N.W., de Zoete, M.R., Flavell, R.A., 2014. Inflammasomes and intestinal homeostasis: regulating and connecting infection, inflammation and the microbiota. Int. Immunol. 26, 495–499. https://doi.org/10.1093/intimm/dxu066

Ghosh, P., Saadat, A., 2021. Neurodegeneration and epigenetics: A review. Neurol. Barc. Spain S0213-4853(21)00034–7. https://doi.org/10.1016/j.nrl.2021.01.016

Gidalevitz, T., Ben-Zvi, A., Ho, K.H., Brignull, H.R., Morimoto, R.I., 2006. Progressive disruption of cellular protein folding in models of polyglutamine diseases. Science 311, 1471–1474. https://doi.org/10.1126/science.1124514

Goldberg, E.L., Shchukina, I., Asher, J.L., Sidorov, S., Artyomov, M.N., Dixit, V.D., 2020. Ketogenesis activates metabolically protective γδ T cells in visceral adipose tissue. Nat. Metab. 2, 50–61. https://doi.org/10.1038/s42255-019-0160-6

Golde, T.E., Miller, V.M., 2009. Proteinopathy-induced neuronal senescence: a hypothesis for brain failure in Alzheimer's and other neurodegenerative diseases. Alzheimers Res. Ther. 1, 5. https://doi.org/10.1186/alzrt5

González, H., Elgueta, D., Montoya, A., Pacheco, R., 2014. Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases. J. Neuroimmunol. 274, 1–13. https://doi.org/10.1016/j.jneuroim.2014.07.012

González, H., Pacheco, R., 2014. T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases. J. Neuroinflammation 11, 201. https://doi.org/10.1186/s12974-014-0201-8

Gorecki, A.M., Preskey, L., Bakeberg, M.C., Kenna, J.E., Gildenhuys, C., MacDougall, G., Dunlop, S.A., Mastaglia, F.L., Akkari, P.A., Koengten, F., Anderton, R.S., 2019. Altered Gut Microbiome in Parkinson's Disease and the Influence of Lipopolysaccharide in a Human α-Synuclein Over-Expressing Mouse Model. Front. Neurosci. 13, 839. https://doi.org/10.3389/fnins.2019.00839

Govindarajan, N., Agis-Balboa, R.C., Walter, J., Sananbenesi, F., Fischer, A., 2011. Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. J. Alzheimers Dis. JAD 26, 187–197. https://doi.org/10.3233/JAD-2011-110080

Greco, V., Longone, P., Spalloni, A., Pieroni, L., Urbani, A., 2019. Crosstalk Between Oxidative Stress and Mitochondrial Damage: Focus on Amyotrophic Lateral Sclerosis. Adv. Exp. Med. Biol. 1158, 71–82. https://doi.org/10.1007/978-981-13-8367-0_5

Green, D.R., Galluzzi, L., Kroemer, G., 2011. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science 333, 1109–1112. https://doi.org/10.1126/science.1201940

Growdon, J.H., Cohen, E.L., Wurtman, R.J., 1977. Huntington's disease: clinical and chemical effects of choline administration. Ann. Neurol. 1, 418–422. https://doi.org/10.1002/ana.410010503

Gu, M., Mei, X.-L., Zhao, Y.-N., 2021. Sepsis and Cerebral Dysfunction: BBB Damage, Neuroinflammation, Oxidative Stress, Apoptosis and Autophagy as Key Mediators and the Potential Therapeutic Approaches. Neurotox. Res. 39, 489–503. https://doi.org/10.1007/s12640-020-00270-5

Guinane, C.M., Cotter, P.D., 2013. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Ther. Adv. Gastroenterol. 6, 295–308. https://doi.org/10.1177/1756283X13482996

Haddadi, R., Nayebi, A.M., Eyvari Brooshghalan, S., 2018. Silymarin prevents apoptosis through inhibiting the Bax/caspase-3 expression and suppresses toll like receptor-4 pathway in the SNc of 6-OHDA intoxicated rats. Biomed. Pharmacother. Biomedecine Pharmacother. 104, 127–136. https://doi.org/10.1016/j.biopha.2018.05.020

Hara, T., Nakamura, K., Matsui, M., Yamamoto, A., Nakahara, Y., Suzuki-Migishima, R., Yokoyama, M., Mishima, K., Saito, I., Okano, H., Mizushima, N., 2006. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441, 885–889. https://doi.org/10.1038/nature04724

Harach, T., Marungruang, N., Duthilleul, N., Cheatham, V., Mc Coy, K.D., Frisoni, G., Neher, J.J., Fåk, F., Jucker, M., Lasser, T., Bolmont, T., 2017. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci. Rep. 7, 41802. https://doi.org/10.1038/srep41802

Haran, J.P., Bhattarai, S.K., Foley, S.E., Dutta, P., Ward, D.V., Bucci, V., McCormick, B.A., 2019. Alzheimer's Disease Microbiome Is Associated with Dysregulation of the Anti-Inflammatory P-Glycoprotein Pathway. mBio 10. https://doi.org/10.1128/mBio.00632-19

Harding, A., Gonder, U., Robinson, S.J., Crean, S., Singhrao, S.K., 2017. Exploring the Association between Alzheimer's Disease, Oral Health, Microbial Endocrinology and Nutrition. Front. Aging Neurosci. 9, 398. https://doi.org/10.3389/fnagi.2017.00398

Hatami, A., Albay, R., Monjazeb, S., Milton, S., Glabe, C., 2014. Monoclonal antibodies against Aβ42 fibrils distinguish multiple aggregation state polymorphisms in vitro and

in Alzheimer disease brain. J. Biol. Chem. 289, 32131–32143. https://doi.org/10.1074/jbc.M114.594846

Heiss, C.N., Olofsson, L.E., 2019. The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. J. Neuroendocrinol. 31, e12684. https://doi.org/10.1111/jne.12684

Hill, J.M., Clement, C., Pogue, A.I., Bhattacharjee, S., Zhao, Y., Lukiw, W.J., 2014. Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). Front. Aging Neurosci. 6. https://doi.org/10.3389/fnagi.2014.00127

Hill, J.M., Lukiw, W.J., 2015. Microbial-generated amyloids and Alzheimer's disease (AD). Front. Aging Neurosci. 7, 9. https://doi.org/10.3389/fnagi.2015.00009

Ho, L., Ono, K., Tsuji, M., Mazzola, P., Singh, R., Pasinetti, G.M., 2018. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev. Neurother. 18, 83–90. https://doi.org/10.1080/14737175.2018.1400909

Hoban, A.E., Stilling, R.M., Ryan, F.J., Shanahan, F., Dinan, T.G., Claesson, M.J., Clarke, G., Cryan, J.F., 2016. Regulation of prefrontal cortex myelination by the microbiota. Transl. Psychiatry 6, e774. https://doi.org/10.1038/tp.2016.42

Hoffman, J.D., Yanckello, L.M., Chlipala, G., Hammond, T.C., McCulloch, S.D., Parikh, I., Sun, S., Morganti, J.M., Green, S.J., Lin, A.-L., 2019. Dietary inulin alters the gut microbiome, enhances systemic metabolism and reduces neuroinflammation in an APOE4 mouse model. PloS One 14, e0221828. https://doi.org/10.1371/journal.pone.0221828

Honda, K., Littman, D.R., 2016. The microbiota in adaptive immune homeostasis and disease. Nature 535, 75–84. https://doi.org/10.1038/nature18848

Hopfner, F., Künstner, A., Müller, S.H., Künzel, S., Zeuner, K.E., Margraf, N.G., Deuschl, G., Baines, J.F., Kuhlenbäumer, G., 2017. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res. 1667, 41–45. https://doi.org/10.1016/j.brainres.2017.04.019

Horai, R., Zárate-Bladés, C.R., Dillenburg-Pilla, P., Chen, J., Kielczewski, J.L., Silver, P.B., Jittayasothorn, Y., Chan, C.-C., Yamane, H., Honda, K., Caspi, R.R., 2015. Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site. Immunity 43, 343–353. https://doi.org/10.1016/j.immuni.2015.07.014

Hoyles, L., Snelling, T., Umlai, U.-K., Nicholson, J.K., Carding, S.R., Glen, R.C., McArthur, S., 2018. Microbiome-host systems interactions: protective effects of propionate upon the blood-brain barrier. Microbiome 6, 55. https://doi.org/10.1186/s40168-018-0439-y

Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., Patterson, P.H., Mazmanian, S.K., 2013. The microbiota modulates gut physiology and behavioral abnormalities associated with autism. Cell 155, 1451–1463. https://doi.org/10.1016/j.cell.2013.11.024

Huang, H., Xu, H., Luo, Q., He, J., Li, M., Chen, H., Tang, W., Nie, Y., Zhou, Y., 2019. Fecal microbiota transplantation to treat Parkinson's disease with constipation: A case report. Medicine (Baltimore) 98, e16163. https://doi.org/10.1097/MD.0000000000016163

Huo, R., Zeng, B., Zeng, L., Cheng, K., Li, B., Luo, Y., Wang, H., Zhou, C., Fang, L., Li, W., Niu, R., Wei, H., Xie, P., 2017. Microbiota Modulate Anxiety-Like Behavior and Endocrine Abnormalities in Hypothalamic-Pituitary-Adrenal Axis. Front. Cell. Infect. Microbiol. 0. https://doi.org/10.3389/fcimb.2017.00489

Iannitti, T., Palmieri, B., 2010. Therapeutical use of probiotic formulations in clinical practice. Clin. Nutr. Edinb. Scotl. 29, 701–725. https://doi.org/10.1016/j.clnu.2010.05.004

Increased intestinal permeability and gut dysbiosis in the R6/2 mouse model of Huntington's disease | Scientific Reports [WWW Document], n.d. URL https://www.nature.com/articles/s41598-020-75229-9 (accessed 2.11.21).

Itzhaki, R.F., Lathe, R., Balin, B.J., Ball, M.J., Bearer, E.L., Braak, H., Bullido, M.J., Carter, C., Clerici, M., Cosby, S.L., Tredici, K.D., Field, H., Fulop, T., Grassi, C., Griffin, W.S.T., Haas, J., Hudson, A.P., Kamer, A.R., Kell, D.B., Licastro, F., Letenneur, L., Lövheim, H., Mancuso, R., Miklossy, J., Otth, C., Palamara, A.T., Perry, G., Preston, C., Pretorius, E., Strandberg, T., Tabet, N., Taylor-Robinson, S.D., Whittum-Hudson, J.A., 2016. Microbes and Alzheimer's Disease. J. Alzheimers Dis. JAD 51, 979–984. https://doi.org/10.3233/JAD-160152

Ivanov, I.I., Atarashi, K., Manel, N., Brodie, E.L., Shima, T., Karaoz, U., Wei, D., Goldfarb, K.C., Santee, C.A., Lynch, S.V., Tanoue, T., Imaoka, A., Itoh, K., Takeda, K., Umesaki, Y., Honda, K., Littman, D.R., 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 139, 485–498. https://doi.org/10.1016/j.cell.2009.09.033

Jang, H.M., Lee, K.E., Kim, D.H., 2018. Immobilization stress-induced Escherichia coli causes anxiety by inducing NF-κB activation through gut microbiota disturbance. Scientific Reports 8, 13897. https://doi.org/10.1038/s41598-018-31764-0

Jangi, S., Gandhi, R., Cox, L.M., Li, N., von Glehn, F., Yan, R., Patel, B., Mazzola, M.A., Liu, S., Glanz, B.L., Cook, S., Tankou, S., Stuart, F., Melo, K., Nejad, P., Smith, K., Topçuolu, B.D., Holden, J., Kivisäkk, P., Chitnis, T., De Jager, P.L., Quintana, F.J., Gerber, G.K., Bry, L., Weiner, H.L., 2016. Alterations of the human gut microbiome in multiple sclerosis. Nat. Commun. 7, 12015. https://doi.org/10.1038/ncomms12015

Jayaraj, R.L., Rodriguez, E.A., Wang, Y., Block, M.L., 2017. Outdoor Ambient Air Pollution and Neurodegenerative Diseases: the Neuroinflammation Hypothesis. Curr. Environ. Health Rep. 4, 166–179. https://doi.org/10.1007/s40572-017-0142-3

Jellinger, K.A., 2010. Basic mechanisms of neurodegeneration: a critical update. J. Cell. Mol. Med. 14, 457–487. https://doi.org/10.1111/j.1582-4934.2010.01010.x

Jenkins, T.A., Nguyen, J.C.D., Polglaze, K.E., Bertrand, P.P., 2016. Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the Gut-Brain Axis. Nutrients 8, E56. https://doi.org/10.3390/nu8010056

Jeon, G.S., Shim, Y.-M., Lee, D.-Y., Kim, J.-S., Kang, M., Ahn, S.H., Shin, J.-Y., Geum, D., Hong, Y.H., Sung, J.-J., 2019. Pathological Modification of TDP-43 in Amyotrophic Lateral Sclerosis with SOD1 Mutations. Mol. Neurobiol. 56, 2007–2021. https://doi.org/10.1007/s12035-018-1218-2

Jin, M., Kalainy, S., Baskota, N., Chiang, D., Deehan, E.C., McDougall, C., Tandon, P., Martínez, I., Cervera, C., Walter, J., Abraldes, J.G., 2019. Faecal microbiota from patients with cirrhosis has a low capacity to ferment non-digestible carbohydrates into short-chain fatty acids. Liver Int. Off. J. Int. Assoc. Study Liver 39, 1437–1447. https://doi.org/10.1111/liv.14106

Jucker, M., Walker, L.C., 2018. Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. Nat. Neurosci. 21, 1341–1349. https://doi.org/10.1038/s41593-018-0238-6

Jucker, M., Walker, L.C., 2011. Pathogenic Protein Seeding in Alzheimer's Disease and Other Neurodegenerative Disorders. Ann. Neurol. 70, 532–540. https://doi.org/10.1002/ana.22615

Juhász, G., Érdi, B., Sass, M., Neufeld, T.P., 2007. Atg7-dependent autophagy promotes neuronal health, stress tolerance, and longevity but is dispensable for metamorphosis in Drosophila. Genes Dev. 21, 3061–3066. https://doi.org/10.1101/gad.1600707

Kabat, A.M., Pott, J., Maloy, K.J., 2016. The Mucosal Immune System and Its Regulation by Autophagy. Front. Immunol. 7. https://doi.org/10.3389/fimmu.2016.00240

Kang, D.-W., Adams, J.B., Coleman, D.M., Pollard, E.L., Maldonado, J., McDonough-Means, S., Caporaso, J.G., Krajmalnik-Brown, R., 2019. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Sci. Rep. 9, 5821. https://doi.org/10.1038/s41598-019-42183-0

Karlsson, C.L.J., Molin, G., Cilio, C.M., Ahrné, S., 2011. The pioneer gut microbiota in human neonates vaginally born at term-a pilot study. Pediatr. Res. 70, 282–286. https://doi.org/10.1203/PDR.0b013e318225f765

Kasubuchi, M., Hasegawa, S., Hiramatsu, T., Ichimura, A., Kimura, I., 2015. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients 7, 2839–2849. https://doi.org/10.3390/nu7042839

Kelly, J.R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., Kennedy, P.J., Beers, S., Scott, K., Moloney, G., Hoban, A.E., Scott, L., Fitzgerald, P., Ross, P., Stanton, C., Clarke, G., Cryan, J.F., Dinan, T.G., 2016. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J. Psychiatr. Res. 82, 109–118. https://doi.org/10.1016/j.jpsychires.2016.07.019

Kelly, J.R., Kennedy, P.J., Cryan, J.F., Dinan, T.G., Clarke, G., Hyland, N.P., 2015. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front. Cell. Neurosci. 9, 392. https://doi.org/10.3389/fncel.2015.00392

Keshavarzian, A., Green, S.J., Engen, P.A., Voigt, R.M., Naqib, A., Forsyth, C.B., Mutlu, E., Shannon, K.M., 2015. Colonic bacterial composition in Parkinson's disease. Mov. Disord. Off. J. Mov. Disord. Soc. 30, 1351–1360. https://doi.org/10.1002/mds.26307

Kikis, E.A., Gidalevitz, T., Morimoto, R.I., 2010. Protein homeostasis in models of aging and age-related conformational disease. Adv. Exp. Med. Biol. 694, 138–159. https://doi.org/10.1007/978-1-4419-7002-2_11

Kim, D.Y., Hao, J., Liu, R., Turner, G., Shi, F.-D., Rho, J.M., 2012. Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. PloS One 7, e35476. https://doi.org/10.1371/journal.pone.0035476

Kim, M., Sandford, E., Gatica, D., Qiu, Y., Liu, X., Zheng, Y., Schulman, B.A., Xu, J., Semple, I., Ro, S.-H., Kim, B., Mavioglu, R.N., Tolun, A., Jipa, A., Takats, S., Karpati, M., Li, J.Z., Yapici, Z., Juhasz, G., Lee, J.H., Klionsky, D.J., Burmeister, M., n.d. Mutation in ATG5 reduces autophagy and leads to ataxia with developmental delay. eLife 5. https://doi.org/10.7554/eLife.12245

Kim, M.-S., Kim, Y., Choi, Hyunjung, Kim, W., Park, S., Lee, D., Kim, D.K., Kim, H.J., Choi, Hayoung, Hyun, D.-W., Lee, J.-Y., Choi, E.Y., Lee, D.-S., Bae, J.-W., Mook-Jung, I., 2020. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut 69, 283–294. https://doi.org/10.1136/gutjnl-2018-317431

Kinney, J.W., Bemiller, S.M., Murtishaw, A.S., Leisgang, A.M., Salazar, A.M., Lamb, B.T., 2018. Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement. N. Y. N 4, 575–590. https://doi.org/10.1016/j.trci.2018.06.014

Kobayashi, A., Hori, K., Yamamoto, T., Yano, M., 2018. Koshihikari: a premium short-grain rice cultivar – its expansion and breeding in Japan. Rice 11, 15. https://doi.org/10.1186/s12284-018-0207-4

Kobayashi, Y., Kinoshita, T., Matsumoto, A., Yoshino, K., Saito, I., Xiao, J.-Z., 2019. Bifidobacterium Breve A1 Supplementation Improved Cognitive Decline in Older Adults with Mild Cognitive Impairment: An Open-Label, Single-Arm Study. J. Prev. Alzheimers Dis. 6, 70–75. https://doi.org/10.14283/jpad.2018.32

Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Tanida, I., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., Tanaka, K., 2006. Loss of autophagy in the central

nervous system causes neurodegeneration in mice. Nature 441, 880–884. https://doi.org/10.1038/nature04723

Kong, G., Cao, K.-A.L., Judd, L.M., Li, S., Renoir, T., Hannan, A.J., 2020. Microbiome profiling reveals gut dysbiosis in a transgenic mouse model of Huntington's disease. Neurobiol. Dis. 135, 104268. https://doi.org/10.1016/j.nbd.2018.09.001

König, J., Wells, J., Cani, P.D., García-Ródenas, C.L., MacDonald, T., Mercenier, A., Whyte, J., Troost, F., Brummer, R.-J., 2016. Human Intestinal Barrier Function in Health and Disease. Clin. Transl. Gastroenterol. 7, e196. https://doi.org/10.1038/ctg.2016.54

Kowalski, K., Mulak, A., 2019. Brain-Gut-Microbiota Axis in Alzheimer's Disease. J. Neurogastroenterol. Motil. 25, 48–60. https://doi.org/10.5056/jnm18087

Kumar, M., Jangra, M., 2012. Does cigarette smoking provoke Parkinson's disease? Int. J. Nutr. Pharmacol. Neurol. Dis. 2, 16. https://doi.org/10.4103/2231-0738.93126

Kuneš, J., Pražienková, V., Popelová, A., Mikulášková, B., Zemenová, J., Maletínská, L., 2016. Prolactin-releasing peptide: a new tool for obesity treatment. J. Endocrinol. 230, R51-58. https://doi.org/10.1530/JOE-16-0046

Lasagna-Reeves, C.A., Castillo-Carranza, D.L., Guerrero-Muoz, M.J., Jackson, G.R., Kayed, R., 2010. Preparation and characterization of neurotoxic tau oligomers. Biochemistry 49, 10039–10041. https://doi.org/10.1021/bi1016233

Lavasani, S., Dzhambazov, B., Nouri, M., Fåk, F., Buske, S., Molin, G., Thorlacius, H., Alenfall, J., Jeppsson, B., Weström, B., 2010. A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PloS One 5, e9009. https://doi.org/10.1371/journal.pone.0009009

Lewis, K., Lutgendorff, F., Phan, V., Söderholm, J.D., Sherman, P.M., McKay, D.M., 2010. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. Inflamm. Bowel Dis. 16, 1138–1148. https://doi.org/10.1002/ibd.21177

Leblhuber, F., Geisler, S., Steiner, K., Fuchs, D., Schütz, B., 2015. Elevated fecal calprotectin in patients with Alzheimer's dementia indicates leaky gut. J. Neural Transm. Vienna Austria 1996 122, 1319–1322. https://doi.org/10.1007/s00702-015-1381-9

Leblhuber, F., Steiner, K., Schuetz, B., Fuchs, D., Gostner, J.M., 2018. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. Curr. Alzheimer Res. 15, 1106–1113. https://doi.org/10.2174/1389200219666180813144834

Lee, Y.K., Menezes, J.S., Umesaki, Y., Mazmanian, S.K., 2011. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A. 108 Suppl 1, 4615–4622. https://doi.org/10.1073/pnas.1000082107

Lesage, S., Brice, A., 2009. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum. Mol. Genet. 18, R48-59. https://doi.org/10.1093/hmg/ddp012

Lévy, J., Cacheux, W., Bara, M.A., L'Hermitte, A., Lepage, P., Fraudeau, M., Trentesaux, C., Lemarchand, J., Durand, A., Crain, A.-M., Marchiol, C., Renault, G., Dumont, F., Letourneur, F., Delacre, M., Schmitt, A., Terris, B., Perret, C., Chamaillard, M., Couty, J.-P., Romagnolo, B., 2015. Intestinal inhibition of Atg7 prevents tumour initiation through a microbiome-influenced immune response and suppresses tumour growth. Nat. Cell Biol. 17, 1062–1073. https://doi.org/10.1038/ncb3206

Levy, M., Kolodziejczyk, A.A., Thaiss, C.A., Elinav, E., 2017. Dysbiosis and the immune system. Nat. Rev. Immunol. 17, 219–232. https://doi.org/10.1038/nri.2017.7

Li, W., Wu, X., Hu, X., Wang, T., Liang, S., Duan, Y., Jin, F., Qin, B., 2017. Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. Sci. China Life Sci. 60, 1223–1233. https://doi.org/10.1007/s11427-016-9001-4

Li, Z., Yi, C.-X., Katiraei, S., Kooijman, S., Zhou, E., Chung, C.K., Gao, Y., van den Heuvel, J.K., Meijer, O.C., Berbée, J.F.P., Heijink, M., Giera, M., Willems van Dijk, K., Groen, A.K., Rensen, P.C.N., Wang, Y., 2018. Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. Gut 67, 1269–1279. https://doi.org/10.1136/gutjnl-2017-314050

Liang, C.-C., Wang, C., Peng, X., Gan, B., Guan, J.-L., 2010. Neural-specific deletion of FIP200 leads to cerebellar degeneration caused by increased neuronal death and axon degeneration. J. Biol. Chem. 285, 3499–3509. https://doi.org/10.1074/jbc.M109.072389

Liang, S., Wu, X., Jin, F., 2018. Gut-Brain Psychology: Rethinking Psychology From the Microbiota–Gut–Brain Axis. Front. Integr. Neurosci. 12. https://doi.org/10.3389/fnint.2018.00033

Lin, M.T., Beal, M.F., 2006. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443, 787–795. https://doi.org/10.1038/nature05292

Ling, D., Song, H.-J., Garza, D., Neufeld, T.P., Salvaterra, P.M., 2009. Abeta42-induced neurodegeneration via an age-dependent autophagic-lysosomal injury in Drosophila. PloS One 4, e4201. https://doi.org/10.1371/journal.pone.0004201

Liu, J., Wang, F., Liu, S., Du, J., Hu, X., Xiong, J., Fang, R., Chen, W., Sun, J., 2017. Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1. J. Neurol. Sci. 381, 176–181. https://doi.org/10.1016/j.jns.2017.08.3235

Liu, Y.-W., Liong, M.T., Chung, Y.-C.E., Huang, H.-Y., Peng, W.-S., Cheng, Y.-F., Lin, Y.-S., Wu, Y.-Y., Tsai, Y.-C., 2019. Effects of Lactobacillus plantarum PS128 on Children with Autism Spectrum Disorder in Taiwan: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients 11. https://doi.org/10.3390/nu11040820

Liu, X.S., Jaenisch, R., 2019. Editing the Epigenome to Tackle Brain Disorders. Trends Neurosci. 42, 861–870. https://doi.org/10.1016/j.tins.2019.10.003

Lopes, F., Keita, Å.V., Saxena, A., Reyes, J.L., Mancini, N.L., Al Rajabi, A., Wang, A., Baggio, C.H., Dicay, M., van Dalen, R., Ahn, Y., Carneiro, M.B.H., Peters, N.C., Rho, J.M., MacNaughton, W.K., Girardin, S.E., Jijon, H., Philpott, D.J., Söderholm, J.D., McKay, D.M., 2018. ER-stress mobilization of death-associated protein kinase-1-dependent xenophagy counteracts mitochondria stress-induced epithelial barrier dysfunction. J. Biol. Chem. 293, 3073–3087. https://doi.org/10.1074/jbc.RA117.000809

López-Valdés, H.E., Martínez-Coria, H., 2016. The Role of Neuroinflammation in Age-Related Dementias. Rev. Investig. Clin. Organo Hosp. Enfermedades Nutr. 68, 40–48.

Louis, P., Flint, H.J., 2009. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol. Lett. 294, 1–8. https://doi.org/10.1111/j.1574-6968.2009.01514.x

Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230. https://doi.org/10.1038/nature11550

Lu, J., Lu, L., Yu, Y., Cluette-Brown, J., Martin, C.R., Claud, E.C., 2018. Effects of Intestinal Microbiota on Brain Development in Humanized Gnotobiotic Mice. Sci. Rep. 8, 5443. https://doi.org/10.1038/s41598-018-23692-w

Lu, Z., Zhang, W., Zhang, N., Jiang, J., Luo, Q., Qiu, Y., 2008. The expression of glutamate transporters in chest compression-induced audiogenic epilepsy: a comparative study. Neurol. Res. 30, 915–919. https://doi.org/10.1179/174313208X327964

Luan, H., Wang, X., Cai, Z., 2019. Mass spectrometry-based metabolomics: Targeting the crosstalk between gut microbiota and brain in neurodegenerative disorders. Mass Spectrom. Rev. 38, 22–33. https://doi.org/10.1002/mas.21553

Luk, K.C., Kehm, V., Carroll, J., Zhang, B., O'Brien, P., Trojanowski, J.Q., Lee, V.M.-Y., 2012. Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice. Science 338, 949–953. https://doi.org/10.1126/science.1227157

Luo, Y., Zeng, B., Zeng, L., Du, X., Li, B., Huo, R., Liu, L., Wang, H., Dong, M., Pan, J., Zheng, P., Zhou, C., Wei, H., Xie, P., 2018. Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. Transl. Psychiatry 8, 187. https://doi.org/10.1038/s41398-018-0240-5

Lynch-Day, M.A., Mao, K., Wang, K., Zhao, M., Klionsky, D.J., 2012. The role of autophagy in Parkinson's disease. Cold Spring Harb. Perspect. Med. 2, a009357. https://doi.org/10.1101/cshperspect.a009357

Lyte, M., 2011. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. BioEssays News Rev. Mol. Cell. Dev. Biol. 33, 574–581. https://doi.org/10.1002/bies.201100024

Maalouf, M.A., Rho, J.M., Mattson, M.P., 2009. THE NEUROPROTECTIVE PROPERTIES OF CALORIE RESTRICTION, THE KETOGENIC DIET, AND KETONE BODIES. Brain Res. Rev. 59, 293–315. https://doi.org/10.1016/j.brainresrev.2008.09.002

MacDonald, M.E., Ambrose, C.M., Duyao, M.P., Myers, R.H., Lin, C., Srinidhi, L., Barnes, G., Taylor, S.A., James, M., Groot, N., MacFarlane, H., Jenkins, B., Anderson, M.A.,

Wexler, N.S., Gusella, J.F., Bates, G.P., Baxendale, S., Hummerich, H., Kirby, S., North, M., Youngman, S., Mott, R., Zehetner, G., Sedlacek, Z., Poustka, A., Frischauf, A.-M., Lehrach, H., Buckler, A.J., Church, D., Doucette-Stamm, L., O'Donovan, M.C., Riba-Ramirez, L., Shah, M., Stanton, V.P., Strobel, S.A., Draths, K.M., Wales, J.L., Dervan, P., Housman, D.E., Altherr, M., Shiang, R., Thompson, L., Fielder, T., Wasmuth, J.J., Tagle, D., Valdes, J., Elmer, L., Allard, M., Castilla, L., Swaroop, M., Blanchard, K., Collins, F.S., Snell, R., Holloway, T., Gillespie, K., Datson, N., Shaw, D., Harper, P.S., 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72, 971–983. https://doi.org/10.1016/0092-8674(93)90585-E

Magistrelli, L., Amoruso, A., Mogna, L., Graziano, T., Cantello, R., Pane, M., Comi, C., 2019. Probiotics May Have Beneficial Effects in Parkinson's Disease: In vitro Evidence. Front. Immunol. 10. https://doi.org/10.3389/fimmu.2019.00969

Makkawi, S., Camara-Lemarroy, C., Metz, L., 2018. Fecal microbiota transplantation associated with 10 years of stability in a patient with SPMS. Neurol. Neuroimmunol. Neuroinflammation 5. https://doi.org/10.1212/NXI.0000000000000459

Manfredsson, F.P., Luk, K.C., Benskey, M.J., Gezer, A., Garcia, J., Kuhn, N.C., Sandoval, I.M., Patterson, J.R., O'Mara, A., Yonkers, R., Kordower, J.H., 2018. Induction of alpha-synuclein pathology in the enteric nervous system of the rat and non-human primate results in gastrointestinal dysmotility and transient CNS pathology. Neurobiol. Dis. 112, 106–118. https://doi.org/10.1016/j.nbd.2018.01.008

Martínez-Lozada, Z., Ortega, A., 2015. Glutamatergic Transmission: A Matter of Three. Neural Plast. 2015, 787396. https://doi.org/10.1155/2015/787396

Marques, T.M., Wall, R., Ross, R.P., Fitzgerald, G.F., Ryan, C.A., Stanton, C., 2010. Programming infant gut microbiota: influence of dietary and environmental factors. Curr. Opin. Biotechnol. 21, 149–156. https://doi.org/10.1016/j.copbio.2010.03.020

Mazzini, L., Mogna, L., De Marchi, F., Amoruso, A., Pane, M., Aloisio, I., Cionci, N.B., Gaggìa, F., Lucenti, A., Bersano, E., Cantello, R., Di Gioia, D., Mogna, G., 2018. Potential Role of Gut Microbiota in ALS Pathogenesis and Possible Novel Therapeutic Strategies. J. Clin. Gastroenterol. 52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition&Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017, S68–S70. https://doi.org/10.1097/MCG.0000000000001042

Mazzoli, R., Pessione, E., 2016. The Neuro-endocrinological Role of Microbial Glutamate and GABA Signaling. Front. Microbiol. 7, 1934. https://doi.org/10.3389/fmicb.2016.01934

McCombe, P.A., Henderson, R.D., Lee, A., Lee, J.D., Woodruff, T.M., Restuadi, R., McRae, A., Wray, N.R., Ngo, S., Steyn, F.J., 2019. Gut microbiota in ALS: possible role in pathogenesis? Expert Rev. Neurother. 19, 785–805. https://doi.org/10.1080/14737175.2019.1623026

McCombe, P.A., Lee, J.D., Woodruff, T.M., Henderson, R.D., 2020. The Peripheral Immune System and Amyotrophic Lateral Sclerosis. Front. Neurol. 11. https://doi.org/10.3389/fneur.2020.00279

McFarlane, H.G., Kusek, G.K., Yang, M., Phoenix, J.L., Bolivar, V.J., Crawley, J.N., 2008. Autism-like behavioral phenotypes in BTBR T+tf/J mice. Genes Brain Behav. 7, 152–163. https://doi.org/10.1111/j.1601-183X.2007.00330.x

McKernan, D.P., Gaszner, G., Quigley, E.M., Cryan, J.F., Dinan, T.G., 2011. Altered peripheral toll-like receptor responses in the irritable bowel syndrome. Aliment. Pharmacol. Ther. 33, 1045–1052. https://doi.org/10.1111/j.1365-2036.2011.04624.x

Medina, M., Avila, J., 2014. The role of extracellular Tau in the spreading of neurofibrillary pathology. Front. Cell. Neurosci. 8. https://doi.org/10.3389/fncel.2014.00113

Medzhitov, R., Janeway, C., 2000. Innate immune recognition: mechanisms and pathways. Immunol. Rev. 173, 89–97. https://doi.org/10.1034/j.1600-065x.2000.917309.x

Mehrabadi, S., Sadr, S.S., 2020. Assessment of Probiotics Mixture on Memory Function, Inflammation Markers, and Oxidative Stress in an Alzheimer's Disease Model of Rats. Iran. Biomed. J. 24, 220–228. https://doi.org/10.29252/ibj.24.4.220

Mestre, L., Carrillo-Salinas, F.J., Mecha, M., Feliú, A., Espejo, C., Álvarez-Cermeño, J.C., Villar, L.M., Guaza, C., 2019. Manipulation of Gut Microbiota Influences Immune Responses, Axon Preservation, and Motor Disability in a Model of Progressive Multiple Sclerosis. Front. Immunol. 10. https://doi.org/10.3389/fimmu.2019.01374

Messenger, J., Clark, S., Massick, S., Bechtel, M., 2013. A review of trimethylaminuria: (fish odor syndrome). J. Clin. Aesthetic Dermatol. 6, 45–48.

Mills, S., Stanton, C., Lane, J.A., Smith, G.J., Ross, R.P., 2019. Precision Nutrition and the Microbiome, Part I: Current State of the Science. Nutrients 11. https://doi.org/10.3390/nu11040923

Minato, T., Maeda, T., Fujisawa, Y., Tsuji, H., Nomoto, K., Ohno, K., Hirayama, M., 2017. Progression of Parkinson's disease is associated with gut dysbiosis: Two-year follow-up study. PloS One 12, e0187307. https://doi.org/10.1371/journal.pone.0187307

Minter, M.R., Taylor, J.M., Crack, P.J., 2016. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. J. Neurochem. 136, 457–474. https://doi.org/10.1111/jnc.13411

Mirzaei, R., Bouzari, B., Hosseini-Fard, S.R., Mazaheri, M., Ahmadyousefi, Y., Abdi, M., Jalalifar, S., Karimitabar, Z., Teimoori, A., Keyvani, H., Zamani, F., Yousefimashouf, R., Karampoor, S., 2021. Role of microbiota-derived short-chain fatty acids in nervous

system disorders. Biomed. Pharmacother. 139, 111661. https://doi.org/10.1016/j.biopha.2021.111661

Mittal, M., Siddiqui, M.R., Tran, K., Reddy, S.P., Malik, A.B., 2014. Reactive Oxygen Species in Inflammation and Tissue Injury. Antioxid. Redox Signal. 20, 1126–1167. https://doi.org/10.1089/ars.2012.5149

Miyake, S., Kim, S., Suda, W., Oshima, K., Nakamura, M., Matsuoka, T., Chihara, N., Tomita, A., Sato, W., Kim, S.-W., Morita, H., Hattori, M., Yamamura, T., 2015. Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with a Striking Depletion of Species Belonging to Clostridia XIVa and IV Clusters. PLoS ONE 10. https://doi.org/10.1371/journal.pone.0137429

Mizushima, N., 2018. A brief history of autophagy from cell biology to physiology and disease. Nat. Cell Biol. 20, 521–527. https://doi.org/10.1038/s41556-018-0092-5

Mizuno, M., Noto, D., Kaga, N., Chiba, A., Miyake, S., 2017. The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. PloS One 12, e0173032. https://doi.org/10.1371/journal.pone.0173032

Mollica, M.P., Mattace Raso, G., Cavaliere, G., Trinchese, G., De Filippo, C., Aceto, S., Prisco, M., Pirozzi, C., Di Guida, F., Lama, A., Crispino, M., Tronino, D., Di Vaio, P., Berni Canani, R., Calignano, A., Meli, R., 2017. Butyrate Regulates Liver Mitochondrial Function, Efficiency, and Dynamics in Insulin-Resistant Obese Mice. Diabetes 66, 1405–1418. https://doi.org/10.2337/db16-0924

Moloney, E.B., de Winter, F., Verhaagen, J., 2014. ALS as a distal axonopathy: molecular mechanisms affecting neuromuscular junction stability in the presymptomatic stages of the disease. Front. Neurosci. 8. https://doi.org/10.3389/fnins.2014.00252

Morris, J.C., Schindler, S.E., McCue, L.M., Moulder, K.L., Benzinger, T.L.S., Cruchaga, C., Fagan, A.M., Grant, E., Gordon, B.A., Holtzman, D.M., Xiong, C., 2019. Assessment

of Racial Disparities in Biomarkers for Alzheimer Disease. JAMA Neurol. 76, 264–273. https://doi.org/10.1001/jamaneurol.2018.4249

Mosca, A., Leclerc, M., Hugot, J.P., 2016. Gut Microbiota Diversity and Human Diseases: Should We Reintroduce Key Predators in Our Ecosystem? Front. Microbiol. 7, 455. https://doi.org/10.3389/fmicb.2016.00455

Mowry, E.M., Glenn, J.D., 2018. The Dynamics of the Gut Microbiome in Multiple Sclerosis in Relation to Disease. Neurol. Clin. 36, 185–196. https://doi.org/10.1016/j.ncl.2017.08.008

Mudd, A.T., Berding, K., Wang, M., Donovan, S.M., Dilger, R.N., 2017. Serum cortisol mediates the relationship between fecal Ruminococcus and brain N-acetylaspartate in the young pig. Gut Microbes 8, 589–600. https://doi.org/10.1080/19490976.2017.1353849

Mudd, A.T., Fleming, S.A., Labhart, B., Chichlowski, M., Berg, B.M., Donovan, S.M., Dilger, R.N., 2017. Dietary Sialyllactose Influences Sialic Acid Concentrations in the Prefrontal Cortex and Magnetic Resonance Imaging Measures in Corpus Callosum of Young Pigs. Nutrients 9. https://doi.org/10.3390/nu9121297

Mukhtar, K., Nawaz, H., Abid, S., 2019. Functional gastrointestinal disorders and gut-brain axis: What does the future hold? World J. Gastroenterol. 25, 552–566. https://doi.org/10.3748/wjg.v25.i5.552

Mulak, A., Bonaz, B., 2015. Brain-gut-microbiota axis in Parkinson's disease. World J. Gastroenterol. 21, 10609–10620. https://doi.org/10.3748/wjg.v21.i37.10609

Murphy, M.M., Guéant, J.-L., 2020. B vitamins and one carbon metabolism micronutrients in health and disease. Biochimie 173, 1–2. https://doi.org/10.1016/j.biochi.2020.04.018

Münch, C., O'Brien, J., Bertolotti, A., 2011. Prion-like propagation of mutant superoxide dismutase-1 misfolding in neuronal cells. Proc. Natl. Acad. Sci. U. S. A. 108, 3548–3553. https://doi.org/10.1073/pnas.1017275108

Musso, G., Gambino, R., Cassader, M., 2011. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. Annu. Rev. Med. 62, 361–380. https://doi.org/10.1146/annurev-med-012510-175505

Nair, A.T., Ramachandran, V., Joghee, N.M., Antony, S., Ramalingam, G., 2018. Gut Microbiota Dysfunction as Reliable Non-invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review. J. Neurogastroenterol. Motil. 24, 30–42. https://doi.org/10.5056/jnm17105

Nataf, S., 2017. Autoimmunity as a Driving Force of Cognitive Evolution. Front. Neurosci. 11. https://doi.org/10.3389/fnins.2017.00582

Ng, Q.X., Soh, A.Y.S., Loke, W., Lim, D.Y., Yeo, W.-S., 2018. The role of inflammation in irritable bowel syndrome (IBS). J. Inflamm. Res. 11, 345–349. https://doi.org/10.2147/JIR.S174982

Ni, F.-F., Li, C.-R., Liao, J.-X., Wang, G.-B., Lin, S.-F., Xia, Y., Wen, J.-L., 2016. The effects of ketogenic diet on the Th17/Treg cells imbalance in patients with intractable childhood epilepsy. Seizure 38, 17–22. https://doi.org/10.1016/j.seizure.2016.03.006

Nielsen, H.H., Qiu, J., Friis, S., Wermuth, L., Ritz, B., 2012. Treatment for Helicobacter pylori infection and risk of Parkinson's disease in Denmark. Eur. J. Neurol. 19, 864–869. https://doi.org/10.1111/j.1468-1331.2011.03643.x

Nighot, P.K., Hu, C.-A.A., Ma, T.Y., 2015. Autophagy enhances intestinal epithelial tight junction barrier function by targeting claudin-2 protein degradation. J. Biol. Chem. 290, 7234–7246. https://doi.org/10.1074/jbc.M114.597492

Nimgampalle, M., Kuna, Y., 2017. Anti-Alzheimer Properties of Probiotic, Lactobacillus plantarum MTCC 1325 in Alzheimer's Disease induced Albino Rats. J. Clin. Diagn. Res. JCDR 11, KC01–KC05. https://doi.org/10.7860/JCDR/2017/26106.10428

Nixon, R.A., 2013. The role of autophagy in neurodegenerative disease. Nat. Med. 19, 983–997. https://doi.org/10.1038/nm.3232

Nixon, R.A., Wegiel, J., Kumar, A., Yu, W.H., Peterhoff, C., Cataldo, A., Cuervo, A.M., 2005. Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. J. Neuropathol. Exp. Neurol. 64, 113–122. https://doi.org/10.1093/jnen/64.2.113

Noack, M., Miossec, P., 2014. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun. Rev. 13, 668–677. https://doi.org/10.1016/j.autrev.2013.12.004

O'Keefe, S.J.D., 2016. Diet, microorganisms and their metabolites, and colon cancer. Nat. Rev. Gastroenterol. Hepatol. 13, 691–706. https://doi.org/10.1038/nrgastro.2016.165

O' Mahony, S.M., Stilling, R.M., Dinan, T.G., Cryan, J.F., 2015. The microbiome and childhood diseases: Focus on brain-gut axis. Birth Defects Res. Part C Embryo Today Rev. 105, 296–313. https://doi.org/10.1002/bdrc.21118

Ochoa-Repáraz, J., Mielcarz, D.W., Ditrio, L.E., Burroughs, A.R., Foureau, D.M., Haque-Begum, S., Kasper, L.H., 2009. Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. J. Immunol. Baltim. Md 1950 183, 6041–6050. https://doi.org/10.4049/jimmunol.0900747

O'Toole, P.W., Jeffery, I.B., 2015. Gut microbiota and aging. Science 350, 1214–1215. https://doi.org/10.1126/science.aac8469

Ou, Z., Deng, L., Lu, Z., Wu, F., Liu, W., Huang, D., Peng, Y., 2020. Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse

model of Alzheimer's disease. Nutr. Diabetes 10, 12. https://doi.org/10.1038/s41387-020-0115-8

Paiva, I., Pinho, R., Pavlou, M.A., Hennion, M., Wales, P., Schütz, A.-L., Rajput, A., Szego, É.M., Kerimoglu, C., Gerhardt, E., Rego, A.C., Fischer, A., Bonn, S., Outeiro, T.F., 2017. Sodium butyrate rescues dopaminergic cells from alpha-synuclein-induced transcriptional deregulation and DNA damage. Hum. Mol. Genet. 26, 2231–2246. https://doi.org/10.1093/hmg/ddx114

Parashar, A., Udayabanu, M., 2017. Gut microbiota: Implications in Parkinson's disease. Parkinsonism Relat. Disord. 38, 1–7. https://doi.org/10.1016/j.parkreldis.2017.02.002

Pasinelli, P., Brown, R.H., 2006. Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nat. Rev. Neurosci. 7, 710–723. https://doi.org/10.1038/nrn1971

Patrick, K.L., Bell, S.L., Weindel, C.G., Watson, R.O., 2019. Exploring the "Multiple-Hit Hypothesis" of Neurodegenerative Disease: Bacterial Infection Comes Up to Bat. Front. Cell. Infect. Microbiol. 9, 138. https://doi.org/10.3389/fcimb.2019.00138

Peelaerts, W., Bousset, L., Van der Perren, A., Moskalyuk, A., Pulizzi, R., Giugliano, M., Van den Haute, C., Melki, R., Baekelandt, V., 2015. α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522, 340–344. https://doi.org/10.1038/nature14547

Perez-Pardo, P., Dodiya, H.B., Engen, P.A., Forsyth, C.B., Huschens, A.M., Shaikh, M., Voigt, R.M., Naqib, A., Green, S.J., Kordower, J.H., Shannon, K.M., Garssen, J., Kraneveld, A.D., Keshavarzian, A., 2019. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut 68, 829–843. https://doi.org/10.1136/gutjnl-2018-316844

Phillips, I.R., Shephard, E.A., 2020. Flavin-containing monooxygenase 3 (FMO3): genetic variants and their consequences for drug metabolism and disease. Xenobiotica Fate

Foreign Compd. Biol. Syst. 50, 19–33. https://doi.org/10.1080/00498254.2019.1643515

Pieragostino, D., Lanuti, P., Cicalini, I., Cufaro, M.C., Ciccocioppo, F., Ronci, M., Simeone, P., Onofrj, M., van der Pol, E., Fontana, A., Marchisio, M., Del Boccio, P., 2019. Proteomics characterization of extracellular vesicles sorted by flow cytometry reveals a disease-specific molecular cross-talk from cerebrospinal fluid and tears in multiple sclerosis. J. Proteomics 204, 103403. https://doi.org/10.1016/j.jprot.2019.103403

Pistollato, F., Sumalla Cano, S., Elio, I., Masias Vergara, M., Giampieri, F., Battino, M., 2016. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr. Rev. 74, 624–634. https://doi.org/10.1093/nutrit/nuw023

Pm, S., Mr, H., N, P., M, M., Ca, G., M, B.-Y., Jn, G., Ws, G., 2013. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis [WWW Document]. Science. https://doi.org/10.1126/science.1241165

Polymenidou, M., Cleveland, D.W., 2012. Prion-like spread of protein aggregates in neurodegeneration. J. Exp. Med. 209, 889–893. https://doi.org/10.1084/jem.20120741

Prusiner, S.B., 2013. Biology and genetics of prions causing neurodegeneration. Annu. Rev. Genet. 47, 601–623. https://doi.org/10.1146/annurev-genet-110711-155524

Prymaczok, N.C., Riek, R., Gerez, J., 2016. More than a Rumor Spreads in Parkinson's Disease. Front. Hum. Neurosci. 10. https://doi.org/10.3389/fnhum.2016.00608

Puig, K.L., Lutz, B.M., Urquhart, S.A., Rebel, A.A., Zhou, X., Manocha, G.D., Sens, M., Tuteja, A.K., Foster, N.L., Combs, C.K., 2015. Overexpression of mutant amyloid-β protein precursor and presenilin 1 modulates enteric nervous system. J. Alzheimers Dis. JAD 44, 1263–1278. https://doi.org/10.3233/JAD-142259

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D.R., Li, J., Xu, J., Li, Shaochuan, Li, D., Cao, J.,

Wang, B., Liang, H., Zheng, H., Xie, Y., Tap, J., Lepage, P., Bertalan, M., Batto, J.-M., Hansen, T., Le Paslier, D., Linneberg, A., Nielsen, H.B., Pelletier, E., Renault, P., Sicheritz-Ponten, T., Turner, K., Zhu, H., Yu, C., Li, Shengting, Jian, M., Zhou, Y., Li, Y., Zhang, X., Li, Songgang, Qin, N., Yang, H., Wang, Jian, Brunak, S., Doré, J., Guarner, F., Kristiansen, K., Pedersen, O., Parkhill, J., Weissenbach, J., Bork, P., Ehrlich, S.D., Wang, Jun, 2010. A human gut microbial gene catalog established by metagenomic sequencing. Nature 464, 59–65. https://doi.org/10.1038/nature08821

Quigley, E.M.M., 2017. Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. Curr. Neurol. Neurosci. Rep. 17, 94. https://doi.org/10.1007/s11910-017-0802-6

R, M., Ld, E., R, D.-E., D, M.-S., Mc, J., J, C., C, S., 2010. Molecular cross talk between misfolded proteins in animal models of Alzheimer's and prion diseases. J. Neurosci. Off. J. Soc. Neurosci. 30, 4528–4535. https://doi.org/10.1523/jneurosci.5924-09.2010

Radde, R., Bolmont, T., Kaeser, S.A., Coomaraswamy, J., Lindau, D., Stoltze, L., Calhoun, M.E., Jäggi, F., Wolburg, H., Gengler, S., Haass, C., Ghetti, B., Czech, C., Hölscher, C., Mathews, P.M., Jucker, M., 2006. Abeta42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. EMBO Rep. 7, 940–946. https://doi.org/10.1038/sj.embor.7400784

Rajilić-Stojanović, M., de Vos, W.M., 2014. The first 1000 cultured species of the human gastrointestinal microbiota. Fems Microbiol. Rev. 38, 996–1047. https://doi.org/10.1111/1574-6976.12075

Ramagopalan, S.V., Dobson, R., Meier, U.C., Giovannoni, G., 2010. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. Lancet Neurol. 9, 727–739. https://doi.org/10.1016/S1474-4422(10)70094-6

Ransohoff, R.M., 2016. How neuroinflammation contributes to neurodegeneration. Science 353, 777–783. https://doi.org/10.1126/science.aag2590

Rao, A.V., Bested, A.C., Beaulne, T.M., Katzman, M.A., Iorio, C., Berardi, J.M., Logan, A.C., 2009. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. Gut Pathog. 1, 6. https://doi.org/10.1186/1757-4749-1-6

Reddy, D.S., Wu, X., Golub, V.M., Dashwood, W.M., Dashwood, R.H., 2018. Measuring Histone Deacetylase Inhibition in the Brain. Curr. Protoc. Pharmacol. 81, e41. https://doi.org/10.1002/cpph.41

Reger, M.A., Henderson, S.T., Hale, C., Cholerton, B., Baker, L.D., Watson, G.S., Hyde, K., Chapman, D., Craft, S., 2004. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. Neurobiol. Aging 25, 311–314. https://doi.org/10.1016/S0197-4580(03)00087-3

Reid, G., Younes, J.A., Van der Mei, H.C., Gloor, G.B., Knight, R., Busscher, H.J., 2011. Microbiota restoration: natural and supplemented recovery of human microbial communities. Nat. Rev. Microbiol. 9, 27–38. https://doi.org/10.1038/nrmicro2473

Rezaei Asl, Z., Sepehri, G., Salami, M., 2019. Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behav. Brain Res. 376, 112183. https://doi.org/10.1016/j.bbr.2019.112183

Rietdijk, C.D., Wezel, R.J.A. van, Garssen, J., Kraneveld, A.D., 2016. Neuronaltoll-like receptors and neuro-immunity in parkinson's disease, Alzheimer's disease and stroke. Neuroimmunol. Neuroinflammation 3, 27–37. https://doi.org/10.20517/2347-8659.2015.28

Rocha, N.P., de Miranda, A.S., Teixeira, A.L., 2015. Insights into Neuroinflammation in Parkinson's Disease: From Biomarkers to Anti-Inflammatory Based Therapies. BioMed Res. Int. 2015, 628192. https://doi.org/10.1155/2015/628192

Rogers, G.B., Keating, D.J., Young, R.L., Wong, M.-L., Licinio, J., Wesselingh, S., 2016. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol. Psychiatry 21, 738–748. https://doi.org/10.1038/mp.2016.50

Rosario, D., Boren, J., Uhlen, M., Proctor, G., Aarsland, D., Mardinoglu, A., Shoaie, S., 2020. Systems Biology Approaches to Understand the Host–Microbiome Interactions in Neurodegenerative Diseases. Front. Neurosci. 14. https://doi.org/10.3389/fnins.2020.00716

Rothhammer, V., Borucki, D.M., Tjon, E.C., Takenaka, M.C., Chao, C.-C., Ardura-Fabregat, A., de Lima, K.A., Gutiérrez-Vázquez, C., Hewson, P., Staszewski, O., Blain, M., Healy, L., Neziraj, T., Borio, M., Wheeler, M., Dragin, L.L., Laplaud, D.A., Antel, J., Alvarez, J.I., Prinz, M., Quintana, F.J., 2018. Microglial control of astrocytes in response to microbial metabolites. Nature 557, 724–728. https://doi.org/10.1038/s41586-018-0119-x

Rothhammer, V., Mascanfroni, I.D., Bunse, L., Takenaka, M.C., Kenison, J.E., Mayo, L., Chao, C.-C., Patel, B., Yan, R., Blain, M., Alvarez, J.I., Kébir, H., Anandasabapathy, N., Izquierdo, G., Jung, S., Obholzer, N., Pochet, N., Clish, C.B., Prinz, M., Prat, A., Antel, J., Quintana, F.J., 2016. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat. Med. 22, 586–597. https://doi.org/10.1038/nm.4106

Round, J.L., Mazmanian, S.K., 2010. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc. Natl. Acad. Sci. U. S. A. 107, 12204–12209. https://doi.org/10.1073/pnas.0909122107

Rowin, J., Xia, Y., Jung, B., Sun, J., 2017. Gut inflammation and dysbiosis in human motor neuron disease. Physiol. Rep. 5. https://doi.org/10.14814/phy2.13443

Rungratanawanich, W., Qu, Y., Wang, X., Essa, M.M., Song, B.-J., 2021. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Exp. Mol. Med. 53, 168–188. https://doi.org/10.1038/s12276-021-00561-7

Saint-Georges-Chaumet, Y., Edeas, M., 2016. Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction. Pathog. Dis. 74, ftv096. https://doi.org/10.1093/femspd/ftv096

Saito, Y., Shioya, A., Sano, T., Sumikura, H., Murata, M., Murayama, S., 2016. Lewy body pathology involves the olfactory cells in Parkinson's disease and related disorders. Mov. Disord. Off. J. Mov. Disord. Soc. 31, 135–138. https://doi.org/10.1002/mds.26463

Salzman, N.H., Hung, K., Haribhai, D., Chu, H., Karlsson-Sjöberg, J., Amir, E., Teggatz, P., Barman, M., Hayward, M., Eastwood, D., Stoel, M., Zhou, Y., Sodergren, E., Weinstock, G.M., Bevins, C.L., Williams, C.B., Bos, N.A., 2010. Enteric defensins are essential regulators of intestinal microbial ecology. Nat. Immunol. 11, 76–83. https://doi.org/10.1038/ni.1825

Sami, N., Rahman, S., Kumar, V., Zaidi, S., Islam, A., Ali, S., Ahmad, F., Hassan, M.I., 2017. Protein aggregation, misfolding and consequential human neurodegenerative diseases. Int. J. Neurosci. 127, 1047–1057. https://doi.org/10.1080/00207454.2017.1286339

Sampson, T.R., Debelius, J.W., Thron, T., Janssen, S., Shastri, G.G., Ilhan, Z.E., Challis, C., Schretter, C.E., Rocha, S., Gradinaru, V., Chesselet, M.-F., Keshavarzian, A., Shannon, K.M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., Mazmanian, S.K., 2016. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell 167, 1469-1480.e12. https://doi.org/10.1016/j.cell.2016.11.018

Sano, C., 2009. History of glutamate production. Am. J. Clin. Nutr. 90, 728S-732S. https://doi.org/10.3945/ajcn.2009.27462F

Sarkar, A., Lehto, S.M., Harty, S., Dinan, T.G., Cryan, J.F., Burnet, P.W.J., 2016. Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends Neurosci. 39, 763–781. https://doi.org/10.1016/j.tins.2016.09.002

Sathiya, S., Ranju, V., Kalaivani, P., Priya, R.J., Sumathy, H., Sunil, A.G., Babu, C.S., 2013. Telmisartan attenuates MPTP induced dopaminergic degeneration and motor dysfunction through regulation of α-synuclein and neurotrophic factors (BDNF and GDNF) expression in C57BL/6J mice. Neuropharmacology 73, 98–110. https://doi.org/10.1016/j.neuropharm.2013.05.025

Savignac, H.M., Corona, G., Mills, H., Chen, L., Spencer, J.P.E., Tzortzis, G., Burnet, P.W.J., 2013. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem. Int. 63, 756–764. https://doi.org/10.1016/j.neuint.2013.10.006

Scheperjans, F., Aho, V., Pereira, P.A.B., Koskinen, K., Paulin, L., Pekkonen, E., Haapaniemi, E., Kaakkola, S., Eerola-Rautio, J., Pohja, M., Kinnunen, E., Murros, K., Auvinen, P., 2015. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov. Disord. Off. J. Mov. Disord. Soc. 30, 350–358. https://doi.org/10.1002/mds.26069

Schmidt, A.C., Leroux, J.-C., 2020. Treatments of trimethylaminuria: where we are and where we might be heading. Drug Discov. Today 25, 1710–1717. https://doi.org/10.1016/j.drudis.2020.06.026

Schneider, S.A., Alcalay, R.N., 2017. Neuropathology of genetic synucleinopathies with parkinsonism: Review of the literature. Mov. Disord. Off. J. Mov. Disord. Soc. 32, 1504–1523. https://doi.org/10.1002/mds.27193

Schönfeld, P., Wojtczak, L., 2016. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. J. Lipid Res. 57, 943–954. https://doi.org/10.1194/jlr.R067629

Schwartz, M., Baruch, K., 2014. The resolution of neuroinflammation in neurodegeneration: leukocyte recruitment via the choroid plexus. EMBO J. 33, 7–22. https://doi.org/10.1002/embj.201386609

Schwartz, M., Deczkowska, A., 2016. Neurological Disease as a Failure of Brain-Immune Crosstalk: The Multiple Faces of Neuroinflammation. Trends Immunol. 37, 668–679. https://doi.org/10.1016/j.it.2016.08.001

Sender, R., Fuchs, S., Milo, R., 2016. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 14. https://doi.org/10.1371/journal.pbio.1002533

Senft, D., Ronai, Z.A., 2015. UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. Trends Biochem. Sci. 40, 141–148. https://doi.org/10.1016/j.tibs.2015.01.002

Sevenich, L., 2018. Brain-Resident Microglia and Blood-Borne Macrophages Orchestrate Central Nervous System Inflammation in Neurodegenerative Disorders and Brain Cancer. Front. Immunol. 9, 697. https://doi.org/10.3389/fimmu.2018.00697

Shaffer, J.J., Ghayoor, A., Long, J.D., Kim, R.E., Lourens, S., O'Donnell, L.J., Westin, C., Rathi, Y., Magnotta, V., Paulsen, J.S., Johnson, H.J., 2017. Longitudinal diffusion changes in prodromal and early HD: Evidence of white-matter tract deterioration. Hum. Brain Mapp. 38, 1460–1477. https://doi.org/10.1002/hbm.23465

Shahi, S.K., Freedman, S.N., Mangalam, A.K., 2017. Gut microbiome in multiple sclerosis: The players involved and the roles they play. Gut Microbes 8, 607–615. https://doi.org/10.1080/19490976.2017.1349041

Sharon, G., Sampson, T.R., Geschwind, D.H., Mazmanian, S.K., 2016. The Central Nervous System and the Gut Microbiome. Cell 167, 915–932. https://doi.org/10.1016/j.cell.2016.10.027

Sherwin, E., Dinan, T.G., Cryan, J.F., 2018. Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann. N. Y. Acad. Sci. 1420, 5–25. https://doi.org/10.1111/nyas.13416

Sherwin, E., Sandhu, K.V., Dinan, T.G., Cryan, J.F., 2016. May the Force Be With You: The Light and Dark Sides of the Microbiota-Gut-Brain Axis in Neuropsychiatry. CNS Drugs 30, 1019–1041. https://doi.org/10.1007/s40263-016-0370-3

Shirooie, S., Nabavi, S.F., Dehpour, A.R., Belwal, T., Habtemariam, S., Argüelles, S., Sureda, A., Daglia, M., Tomczyk, M., Sobarzo-Sanchez, E., Xu, S., Nabavi, S.M., 2018. Targeting mTORs by omega-3 fatty acids: A possible novel therapeutic strategy for neurodegeneration? Pharmacol. Res. 135, 37–48. https://doi.org/10.1016/j.phrs.2018.07.004

Silva, Y.P., Bernardi, A., Frozza, R.L., 2020. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front. Endocrinol. 11, 25. https://doi.org/10.3389/fendo.2020.00025

Singh, V., Roth, S., Llovera, G., Sadler, R., Garzetti, D., Stecher, B., Dichgans, M., Liesz, A., 2016. Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J. Neurosci. 36, 7428–7440. https://doi.org/10.1523/JNEUROSCI.1114-16.2016

Siniscalco, D., Schultz, S., Brigida, A.L., Antonucci, N., 2018. Inflammation and Neuro-Immune Dysregulations in Autism Spectrum Disorders. Pharm. Basel Switz. 11. https://doi.org/10.3390/ph11020056

Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin. Neurosci. 8, 383–395.

Soeiro-de-Souza, M.G., Henning, A., Machado-Vieira, R., Moreno, R.A., Pastorello, B.F., da Costa Leite, C., Vallada, H., Otaduy, M.C.G., 2015. Anterior cingulate Glutamate-Glutamine cycle metabolites are altered in euthymic bipolar I disorder. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 2221–2229. https://doi.org/10.1016/j.euroneuro.2015.09.020

Soliman, M.L., Combs, C.K., Rosenberger, T.A., 2013. Modulation of inflammatory cytokines and mitogen-activated protein kinases by acetate in primary astrocytes. J. Neuroimmune Pharmacol. Off. J. Soc. NeuroImmune Pharmacol. 8, 287–300. https://doi.org/10.1007/s11481-012-9426-4

Soliman, M.L., Puig, K.L., Combs, C.K., Rosenberger, T.A., 2012. Acetate reduces microglia inflammatory signaling in vitro. J. Neurochem. 123, 555–567. https://doi.org/10.1111/j.1471-4159.2012.07955.x

Solleiro-Villavicencio, H., Rivas-Arancibia, S., 2018. Effect of Chronic Oxidative Stress on Neuroinflammatory Response Mediated by CD4+T Cells in Neurodegenerative Diseases. Front. Cell. Neurosci. 12, 114. https://doi.org/10.3389/fncel.2018.00114

Soto, C., Pritzkow, S., 2018. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat. Neurosci. 21, 1332–1340. https://doi.org/10.1038/s41593-018-0235-9

Staley, C., Khoruts, A., Sadowsky, M.J., 2017. Contemporary Applications of Fecal Microbiota Transplantation to Treat Intestinal Diseases in Humans. Arch. Med. Res. 48, 766–773. https://doi.org/10.1016/j.arcmed.2017.11.006

Stanisavljević, S., Lukić, J., Soković, S., Mihajlovic, S., Mostarica Stojković, M., Miljković, D., Golić, N., 2016. Correlation of Gut Microbiota Composition with Resistance to Experimental Autoimmune Encephalomyelitis in Rats. Front. Microbiol. 7. https://doi.org/10.3389/fmicb.2016.02005

Stilling, R.M., Cryan, J.F., 2016. Host response: A trigger for neurodegeneration? Nat. Microbiol. 1, 1–2. https://doi.org/10.1038/nmicrobiol.2016.129

Sudo, N., 2014. Microbiome, HPA axis and production of endocrine hormones in the gut. Adv. Exp. Med. Biol. 817, 177–194. https://doi.org/10.1007/978-1-4939-0897-4_8

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.-N., Kubo, C., Koga, Y., 2004. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J. Physiol. 558, 263–275. https://doi.org/10.1113/jphysiol.2004.063388

Sun, J., Xu, J., Ling, Y., Wang, F., Gong, T., Yang, C., Ye, S., Ye, K., Wei, D., Song, Z., Chen, D., Liu, J., 2019. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl. Psychiatry 9. https://doi.org/10.1038/s41398-019-0525-3

Sun, M.-F., Zhu, Y.-L., Zhou, Z.-L., Jia, X.-B., Xu, Y.-D., Yang, Q., Cui, C., Shen, Y.-Q., 2018. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: Gut microbiota, glial reaction and TLR4/TNF-α signaling pathway. Brain. Behav. Immun. 70, 48–60. https://doi.org/10.1016/j.bbi.2018.02.005

Szentirmai, É., Millican, N.S., Massie, A.R., Kapás, L., 2019. Butyrate, a metabolite of intestinal bacteria, enhances sleep. Sci. Rep. 9, 7035. https://doi.org/10.1038/s41598-019-43502-1

Tamtaji, O.R., Heidari-Soureshjani, R., Mirhosseini, N., Kouchaki, E., Bahmani, F., Aghadavod, E., Tajabadi-Ebrahimi, M., Asemi, Z., 2019a. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. Clin. Nutr. Edinb. Scotl. 38, 2569–2575. https://doi.org/10.1016/j.clnu.2018.11.034

Tamtaji, O.R., Taghizadeh, M., Daneshvar Kakhaki, R., Kouchaki, E., Bahmani, F., Borzabadi, S., Oryan, S., Mafi, A., Asemi, Z., 2019b. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: A randomized, double-blind, placebo-controlled trial. Clin. Nutr. Edinb. Scotl. 38, 1031–1035. https://doi.org/10.1016/j.clnu.2018.05.018019-43502-1

Tan, J., McKenzie, C., Potamitis, M., Thorburn, A.N., Mackay, C.R., Macia, L., 2014. The role of short-chain fatty acids in health and disease. Adv. Immunol. 121, 91–119. https://doi.org/10.1016/B978-0-12-800100-4.00003-9

Tanca, A., Palomba, A., Fraumene, C., Manghina, V., Silverman, M., Uzzau, S., 2018. Clostridial Butyrate Biosynthesis Enzymes Are Significantly Depleted in the Gut Microbiota of Nonobese Diabetic Mice. mSphere 3. https://doi.org/10.1128/mSphere.00492-18

Tankou, S.K., Regev, K., Healy, B.C., Cox, L.M., Tjon, E., Kivisakk, P., Vanande, I.P., Cook, S., Gandhi, R., Glanz, B., Stankiewicz, J., Weiner, H.L., 2018a. Investigation of probiotics in multiple sclerosis. Mult. Scler. Houndmills Basingstoke Engl. 24, 58–63. https://doi.org/10.1177/1352458517737390

Tankou, S.K., Regev, K., Healy, B.C., Tjon, E., Laghi, L., Cox, L.M., Kivisäkk, P., Pierre, I.V., Hrishikesh, L., Gandhi, R., Cook, S., Glanz, B., Stankiewicz, J., Weiner, H.L., 2018b. A probiotic modulates the microbiome and immunity in multiple sclerosis. Ann. Neurol. 83, 1147–1161. https://doi.org/10.1002/ana.25244

Tanous, C., Chambellon, E., Sepulchre, A.-M., Yvon, M., 2005. The Gene Encoding the Glutamate Dehydrogenase in Lactococcus lactis Is Part of a Remnant Tn3 Transposon Carried by a Large Plasmid. J. Bacteriol. 187, 5019–5022. https://doi.org/10.1128/JB.187.14.5019-5022.2005

Tawiah, A., Cornick, S., Moreau, F., Gorman, H., Kumar, M., Tiwari, S., Chadee, K., 2018. High MUC2 Mucin Expression and Misfolding Induce Cellular Stress, Reactive Oxygen Production, and Apoptosis in Goblet Cells. Am. J. Pathol. 188, 1354–1373. https://doi.org/10.1016/j.ajpath.2018.02.007

Taylor-Walker, G., Lynn, S.A., Keeling, E., Munday, R., Johnston, D.A., Page, A., Scott, J.A., Goverdhan, S., Lotery, A.J., Ratnayaka, J.A., 2016. The Alzheimer's-related amyloid beta peptide is internalised by R28 neuroretinal cells and disrupts the microtubule associated protein 2 (MAP-2). Exp. Eye Res. 153, 110–121. https://doi.org/10.1016/j.exer.2016.10.013

Teltschik, Z., Wiest, R., Beisner, J., Nuding, S., Hofmann, C., Schoelmerich, J., Bevins, C.L., Stange, E.F., Wehkamp, J., 2012. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. Hepatol. Baltim. Md 55, 1154–1163. https://doi.org/10.1002/hep.24789

Teo, R.T.Y., Ferrari Bardile, C., Tay, Y.L., Yusof, N.A.B.M., Kreidy, C.A., Tan, L.J., Pouladi, M.A., 2019. Impaired Remyelination in a Mouse Model of Huntington Disease. Mol. Neurobiol. 56, 6873–6882. https://doi.org/10.1007/s12035-019-1579-1

Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J.C., Verschoor, C.P., Loukov, D., Schenck, L.P., Jury, J., Foley, K.P., Schertzer, J.D., Larché, M.J., Davidson, D.J., Verdú, E.F., Surette, M.G., Bowdish, D.M.E., 2017. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe 21, 455-466.e4. https://doi.org/10.1016/j.chom.2017.03.002

Tilg, H., Zmora, N., Adolph, T.E., Elinav, E., 2020. The intestinal microbiota fuelling metabolic inflammation. Nat. Rev. Immunol. 20, 40–54. https://doi.org/10.1038/s41577-019-0198-4

Ton, A.M.M., Campagnaro, B.P., Alves, G.A., Aires, R., Côco, L.Z., Arpini, C.M., Guerra e Oliveira, T., Campos-Toimil, M., Meyrelles, S.S., Pereira, T.M.C., Vasquez, E.C., 2020. Oxidative Stress and Dementia in Alzheimer's Patients: Effects of Synbiotic Supplementation [WWW Document]. Oxid. Med. Cell. Longev. https://doi.org/10.1155/2020/2638703

Torres-Fuentes, C., Golubeva, A.V., Zhdanov, A.V., Wallace, S., Arboleya, S., Papkovsky, D.B., El Aidy, S., Ross, P., Roy, B.L., Stanton, C., Dinan, T.G., Cryan, J.F., Schellekens, H., 2019. Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 33, 13546–13559. https://doi.org/10.1096/fj.201901433R

Tremlett, H., Bauer, K.C., Appel-Cresswell, S., Finlay, B.B., Waubant, E., 2017. The gut microbiome in human neurological disease: A review. Ann. Neurol. 81, 369–382. https://doi.org/10.1002/ana.24901

Tremlett, H., Fadrosh, D.W., Faruqi, A.A., Zhu, F., Hart, J., Roalstad, S., Graves, J., Lynch, S., Waubant, E., US Network of Pediatric MS Centers, 2016. Gut microbiota in early pediatric multiple sclerosis: a case-control study. Eur. J. Neurol. 23, 1308–1321. https://doi.org/10.1111/ene.13026

Tremlett, H., Waubant, E., 2018. Gut microbiome and pediatric multiple sclerosis. Mult. Scler. Houndmills Basingstoke Engl. 24, 64–68. https://doi.org/10.1177/1352458517737369

Truax, A.D., Chen, L., Tam, J.W., Cheng, N., Guo, H., Koblansky, A.A., Chou, W.-C., Wilson, J.E., Brickey, W.J., Petrucelli, A., Liu, R., Cooper, D.E., Koenigsknecht, M.J., Young, V.B., Netea, M.G., Stienstra, R., Sartor, R.B., Montgomery, S.A., Coleman, R.A., Ting, J.P.-Y., 2018. The inhibitory innate immune sensor NLRP12 maintains a threshold against obesity by regulating gut microbiota homeostasis. Cell Host Microbe 24, 364-378.e6. https://doi.org/10.1016/j.chom.2018.08.009

Tsuboi, K., Nishitani, M., Takakura, A., Imai, Y., Komatsu, M., Kawashima, H., 2015. Autophagy Protects against Colitis by the Maintenance of Normal Gut Microflora and Secretion of Mucus. J. Biol. Chem. 290, 20511–20526. https://doi.org/10.1074/jbc.M114.632257

Tükel, Ç., Nishimori, J.H., Wilson, R.P., Winter, M.G., Keestra, A.M., van Putten, J.P.M., Bäumler, A.J., 2010. Toll-like receptors 1 and 2 cooperatively mediate immune responses to curli, a common amyloid from enterobacterial biofilms. Cell. Microbiol. 12. https://doi.org/10.1111/j.1462-5822.2010.01485.x

Tükel, Ç., Wilson, R.P., Nishimori, J.H., Pezeshki, M., Chromy, B.A., Bäumler, A.J., 2009. Responses to amyloids of microbial and host origin are mediated through Toll-like receptor 2. Cell Host Microbe 6, 45–53. https://doi.org/10.1016/j.chom.2009.05.020

Tyler Patterson, T., Grandhi, R., 2020. Gut Microbiota and Neurologic Diseases and Injuries. Adv. Exp. Med. Biol. 1238, 73–91. https://doi.org/10.1007/978-981-15-2385-4_6

Tysnes, O.-B., Storstein, A., 2017. Epidemiology of Parkinson's disease. J. Neural Transm. Vienna Austria 1996 124, 901–905. https://doi.org/10.1007/s00702-017-1686-y

Uesaka, T., Young, H.M., Pachnis, V., Enomoto, H., 2016. Development of the intrinsic and extrinsic innervation of the gut. Dev. Biol. 417, 158–167. https://doi.org/10.1016/j.ydbio.2016.04.016

Ugalde, C.L., Annesley, S.J., Gordon, S.E., Mroczek, K., Perugini, M.A., Lawson, V.A., Fisher, P.R., Finkelstein, D.I., Hill, A.F., 2020. Misfolded α-synuclein causes hyperactive respiration without functional deficit in live neuroblastoma cells. Dis. Model. Mech. 13. https://doi.org/10.1242/dmm.040899

Ugalde, C.L., Finkelstein, D.I., Lawson, V.A., Hill, A.F., 2016. Pathogenic mechanisms of prion protein, amyloid-β and α-synuclein misfolding: the prion concept and

neurotoxicity of protein oligomers. J. Neurochem. 139, 162–180. https://doi.org/10.1111/jnc.13772

Unger, M.M., Spiegel, J., Dillmann, K.-U., Grundmann, D., Philippeit, H., Bürmann, J., Faßbender, K., Schwiertz, A., Schäfer, K.-H., 2016. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat. Disord. 32, 66–72. https://doi.org/10.1016/j.parkreldis.2016.08.019

Vakharia, K., Hinson, J.P., 2005. Lipopolysaccharide directly stimulates cortisol secretion by human adrenal cells by a cyclooxygenase-dependent mechanism. Endocrinology 146, 1398–1402. https://doi.org/10.1210/en.2004-0882

Vaishampayan, P.A., Kuehl, J.V., Froula, J.L., Morgan, J.L., Ochman, H., Francino, M.P., 2010. Comparative metagenomics and population dynamics of the gut microbiota in mother and infant. Genome Biol. Evol. 2, 53–66. https://doi.org/10.1093/gbe/evp057

Vallès, Y., Gosalbes, M.J., Vries, L.E. de, Abellán, J.J., Francino, M.P., 2012. Metagenomics and development of the gut microbiota in infants. Clin. Microbiol. Infect. 18, 21–26. https://doi.org/10.1111/j.1469-0691.2012.03876.x

van Bodegom, M., Homberg, J.R., Henckens, M.J.A.G., 2017. Modulation of the Hypothalamic-Pituitary-Adrenal Axis by Early Life Stress Exposure. Front. Cell. Neurosci. 11, 87. https://doi.org/10.3389/fncel.2017.00087

van der Burg, J.M.M., Winqvist, A., Aziz, N.A., Maat-Schieman, M.L.C., Roos, R.A.C., Bates, G.P., Brundin, P., Björkqvist, M., Wierup, N., 2011. Gastrointestinal dysfunction contributes to weight loss in Huntington's disease mice. Neurobiol. Dis. 44, 1–8. https://doi.org/10.1016/j.nbd.2011.05.006

Vanitallie, T.B., Nonas, C., Di Rocco, A., Boyar, K., Hyams, K., Heymsfield, S.B., 2005. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 64, 728–730. https://doi.org/10.1212/01.WNL.0000152046.11390.45

Varela, R.B., Valvassori, S.S., Lopes-Borges, J., Mariot, E., Dal-Pont, G.C., Amboni, R.T., Bianchini, G., Quevedo, J., 2015. Sodium butyrate and mood stabilizers block ouabain-induced hyperlocomotion and increase BDNF, NGF and GDNF levels in brain of Wistar rats. J. Psychiatr. Res. 61, 114–121. https://doi.org/10.1016/j.jpsychires.2014.11.003

Verwaest, K.A., Vu, T.N., Laukens, K., Clemens, L.E., Nguyen, H.P., Van Gasse, B., Martins, J.C., Van Der Linden, A., Dommisse, R., 2011. (1)H NMR based metabolomics of CSF and blood serum: a metabolic profile for a transgenic rat model of Huntington disease. Biochim. Biophys. Acta 1812, 1371–1379. https://doi.org/10.1016/j.bbadis.2011.08.001

Vijay, N., Morris, M.E., 2014. Role of monocarboxylate transporters in drug delivery to the brain. Curr. Pharm. Des. 20, 1487–1498. https://doi.org/10.2174/13816128113199990462

Visanji, N.P., Brooks, P.L., Hazrati, L.-N., Lang, A.E., 2013. The prion hypothesis in Parkinson's disease: Braak to the future. Acta Neuropathol. Commun. 1, 2. https://doi.org/10.1186/2051-5960-1-2

Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A., Harding, S.J., Merluzzi, A.P., Johnson, S.C., Carlsson, C.M., Asthana, S., Zetterberg, H., Blennow, K., Bendlin, B.B., Rey, F.E., 2017. Gut microbiome alterations in Alzheimer's disease. Sci. Rep. 7, 13537. https://doi.org/10.1038/s41598-017-13601-y

Vulevic, J., Juric, A., Walton, G.E., Claus, S.P., Tzortzis, G., Toward, R.E., Gibson, G.R., 2015. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota,

immune parameters and metabonomics in elderly persons. Br. J. Nutr. 114, 586–595. https://doi.org/10.1017/S0007114515001889

Walker, L.C., Jucker, M., 2015. Neurodegenerative diseases: expanding the prion concept. Annu. Rev. Neurosci. 38, 87–103. https://doi.org/10.1146/annurev-neuro-071714-033828

Wang, D., Ho, L., Faith, J., Ono, K., Janle, E.M., Lachcik, P.J., Cooper, B.R., Jannasch, A.H., D'Arcy, B.R., Williams, B.A., Ferruzzi, M.G., Levine, S., Zhao, W., Dubner, L., Pasinetti, G.M., 2015. Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease β-amyloid oligomerization. Mol. Nutr. Food Res. 59, 1025–1040. https://doi.org/10.1002/mnfr.201400544

Wang, P., Zhang, Y., Gong, Y., Yang, R., Chen, Z., Hu, W., Wu, Y., Gao, M., Xu, X., Qin, Y., Huang, C., 2018. Sodium butyrate triggers a functional elongation of microglial process via Akt-small RhoGTPase activation and HDACs inhibition. Neurobiol. Dis. 111, 12–25. https://doi.org/10.1016/j.nbd.2017.12.006

Wang, Yudong, Palmfeldt, J., Gregersen, N., Makhov, A.M., Conway, J.F., Wang, M., McCalley, S.P., Basu, S., Alharbi, H., Croix, C.S., Calderon, M.J., Watkins, S., Vockley, J., 2019. Mitochondrial fatty acid oxidation and the electron transport chain comprise a multifunctional mitochondrial protein complex. J. Biol. Chem. 294, 12380–12391. https://doi.org/10.1074/jbc.RA119.008680

Wang, Yan, Xu, E., Musich, P.R., Lin, F., 2019. Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. CNS Neurosci. Ther. 25, 816–824. https://doi.org/10.1111/cns.13116

Wang, Z., Roberts, A.B., Buffa, J.A., Levison, B.S., Zhu, W., Org, E., Gu, X., Huang, Y., Zamanian-Daryoush, M., Culley, M.K., DiDonato, A.J., Fu, X., Hazen, J.E., Krajcik,

D., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2015. Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis. Cell 163, 1585–1595. https://doi.org/10.1016/j.cell.2015.11.055

Wasser, C.I., Mercieca, E.-C., Kong, G., Hannan, A.J., McKeown, S.J., Glikmann-Johnston, Y., Stout, J.C., 2020. Gut dysbiosis in Huntington's disease: associations among gut microbiota, cognitive performance and clinical outcomes. Brain Commun. 2. https://doi.org/10.1093/braincomms/fcaa110

Watt, R., Parkin, K., Martino, D., 2020. The Potential Effects of Short-Chain Fatty Acids on the Epigenetic Regulation of Innate Immune Memory. Challenges 11, 25. https://doi.org/10.3390/challe11020025

Wekerle, H., 2018. Brain inflammatory cascade controlled by gut-derived molecules. Nature 557, 642–643. https://doi.org/10.1038/d41586-018-05113-0

Wells, J.M., Brummer, R.J., Derrien, M., MacDonald, T.T., Troost, F., Cani, P.D., Theodorou, V., Dekker, J., Méheust, A., de Vos, W.M., Mercenier, A., Nauta, A., Garcia-Rodenas, C.L., 2017. Homeostasis of the gut barrier and potential biomarkers. Am. J. Physiol. Gastrointest. Liver Physiol. 312, G171–G193. https://doi.org/10.1152/ajpgi.00048.2015

Westfall, S., Lomis, N., Prakash, S., 2019. A novel synbiotic delays Alzheimer's disease onset via combinatorial gut-brain-axis signaling in Drosophila melanogaster. PLoS ONE 14. https://doi.org/10.1371/journal.pone.0214985

Wilson, C.A., Murphy, D.D., Giasson, B.I., Zhang, B., Trojanowski, J.Q., Lee, V.M.-Y., 2004. Degradative organelles containing mislocalized α- and β-synuclein proliferate in presenilin-1 null neurons. J. Cell Biol. 165, 335–346. https://doi.org/10.1083/jcb.200403061

Wilson, R.S., Leurgans, S.E., Boyle, P.A., Schneider, J.A., Bennett, D.A., 2010. Neurodegenerative basis of age-related cognitive decline (e–Pub ahead of print)(CME). Neurology 75, 1070–1078. https://doi.org/10.1212/WNL.0b013e3181f39adc

Wilton, D.K., Dissing-Olesen, L., Stevens, B., 2019. Neuron-Glia Signaling in Synapse Elimination. Annu. Rev. Neurosci. 42, 107–127. https://doi.org/10.1146/annurev-neuro-070918-050306

Włodarek, D., 2019. Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). Nutrients 11. https://doi.org/10.3390/nu11010169

Wright, M.L., Fournier, C., Houser, M.C., Tansey, M., Glass, J., Hertzberg, V.S., 2018. Potential Role of the Gut Microbiome in ALS: A Systematic Review. Biol. Res. Nurs. 20, 513–521. https://doi.org/10.1177/1099800418784202

Wu, S., Yi, J., Zhang, Y.-G., Zhou, J., Sun, J., 2015. Leaky intestine and impaired microbiome in an amyotrophic lateral sclerosis mouse model. Physiol. Rep. 3. https://doi.org/10.14814/phy2.12356

Xu, R., Wang, Q., 2016. Towards understanding brain-gut-microbiome connections in Alzheimer's disease. BMC Syst. Biol. 10, 63. https://doi.org/10.1186/s12918-016-0307-y

Xu, X., Araki, K., Li, S., Han, J.-H., Ye, L., Tan, W.G., Konieczny, B.T., Bruinsma, M.W., Martinez, J., Pearce, E.L., Green, D.R., Jones, D.P., Virgin, H.W., Ahmed, R., 2014. Autophagy is essential for effector CD8(+) T cell survival and memory formation. Nat. Immunol. 15, 1152–1161. https://doi.org/10.1038/ni.3025

Yamada, K., Cirrito, J.R., Stewart, F.R., Jiang, H., Finn, M.B., Holmes, B.B., Binder, L.I., Mandelkow, E.-M., Diamond, M.I., Lee, V.M.-Y., Holtzman, D.M., 2011. In Vivo Microdialysis Reveals Age-Dependent Decrease of Brain Interstitial Fluid Tau Levels

in P301S Human Tau Transgenic Mice. J. Neurosci. 31, 13110–13117. https://doi.org/10.1523/JNEUROSCI.2569-11.2011

Yamawaki, Y., Yoshioka, N., Nozaki, K., Ito, H., Oda, K., Harada, K., Shirawachi, S., Asano, S., Aizawa, H., Yamawaki, S., Kanematsu, T., Akagi, H., 2018. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res. 1680, 13–38. https://doi.org/10.1016/j.brainres.2017.12.004

Yang, D.-S., Stavrides, P., Mohan, P.S., Kaushik, S., Kumar, A., Ohno, M., Schmidt, S.D., Wesson, D., Bandyopadhyay, U., Jiang, Y., Pawlik, M., Peterhoff, C.M., Yang, A.J., Wilson, D.A., St George-Hyslop, P., Westaway, D., Mathews, P.M., Levy, E., Cuervo, A.M., Nixon, R.A., 2011. Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. Brain J. Neurol. 134, 258–277. https://doi.org/10.1093/brain/awq341

Yang, L., Liu, C., Zhao, W., He, C., Ding, J., Dai, R., Xu, K., Xiao, L., Luo, L., Liu, S., Li, W., Meng, H., 2018. Impaired Autophagy in Intestinal Epithelial Cells Alters Gut Microbiota and Host Immune Responses. Appl. Environ. Microbiol. 84. https://doi.org/10.1128/AEM.00880-18

Yang, L.L., Millischer, V., Rodin, S., MacFabe, D.F., Villaescusa, J.C., Lavebratt, C., 2020. Enteric short-chain fatty acids promote proliferation of human neural progenitor cells. J. Neurochem. 154, 635–646. https://doi.org/10.1111/jnc.14928

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., 2015. Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell 161, 264–276. https://doi.org/10.1016/j.cell.2015.02.047

Zareian, M., Ebrahimpour, A., Bakar, F.A., Mohamed, A.K.S., Forghani, B., Ab-Kadir, M.S.B., Saari, N., 2012. A glutamic acid-producing lactic acid bacteria isolated from Malaysian fermented foods. Int. J. Mol. Sci. 13, 5482–5497. https://doi.org/10.3390/ijms13055482

Zeng, Q., Shen, J., Chen, K., Zhou, J., Liao, Q., Lu, K., Yuan, J., Bi, F., 2020. The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients. Sci. Rep. 10. https://doi.org/10.1038/s41598-020-69845-8

Zeraati, M., Enayati, M., Kafami, L., Shahidi, S.H., Salari, A.-A., 2019. Gut microbiota depletion from early adolescence alters adult immunological and neurobehavioral responses in a mouse model of multiple sclerosis. Neuropharmacology 157, 107685. https://doi.org/10.1016/j.neuropharm.2019.107685

Zhai, C.-D., Zheng, J.-J., An, B.-C., Huang, H.-F., Tan, Z.-C., 2019. Intestinal microbiota composition in patients with amyotrophic lateral sclerosis: establishment of bacterial and archaeal communities analyses. Chin. Med. J. (Engl.) 132, 1815–1822. https://doi.org/10.1097/CM9.0000000000000351

Zhan, X., Stamova, B., Jin, L.-W., DeCarli, C., Phinney, B., Sharp, F.R., 2016. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology 87, 2324–2332. https://doi.org/10.1212/WNL.0000000000003391

Zhang, C., Yan, J., Xiao, Y., Shen, Y., Wang, J., Ge, W., Chen, Y., 2017. Inhibition of Autophagic Degradation Process Contributes to Claudin-2 Expression Increase and Epithelial Tight Junction Dysfunction in TNF-α Treated Cell Monolayers. Int. J. Mol. Sci. 18. https://doi.org/10.3390/ijms18010157

Zhang, F., Yue, L., Fang, X., Wang, G., Li, C., Sun, X., Jia, X., Yang, J., Song, J., Zhang, Y., Guo, C., Ma, G., Sang, M., Chen, F., Wang, P., 2020. Altered gut microbiota in Parkinson's disease patients/healthy spouses and its association with clinical features.

Parkinsonism Relat. Disord. 81, 84–88. https://doi.org/10.1016/j.parkreldis.2020.10.034

Zhang, L.S., Davies, S.S., 2016. Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome Med. 8. https://doi.org/10.1186/s13073-016-0296-x

Zhang, T., Yang, S., Du, J., 2014. Protective Effects of Berberine on Isoproterenol-Induced Acute Myocardial Ischemia in Rats through Regulating HMGB1-TLR4 Axis. Evid.-Based Complement. Altern. Med. ECAM 2014. https://doi.org/10.1155/2014/849783

Zhang, Y.-G., Wu, S., Yi, J., Xia, Y., Jin, D., Zhou, J., Sun, J., 2017. Target Intestinal Microbiota to Alleviate Disease Progression in Amyotrophic Lateral Sclerosis. Clin. Ther. 39, 322–336. https://doi.org/10.1016/j.clinthera.2016.12.014

Zhang, Z., Hou, L., Song, J.-L., Song, N., Sun, Y.-J., Lin, X., Wang, X.-L., Zhang, F.-Z., Ge, Y.-L., 2014. Pro-inflammatory cytokine-mediated ferroportin down-regulation contributes to the nigral iron accumulation in lipopolysaccharide-induced Parkinsonian models. Neuroscience 257, 20–30. https://doi.org/10.1016/j.neuroscience.2013.09.037

Zhao, H., Gao, X., Xi, L., Shi, Y., Peng, L., Wang, C., Zou, L., Yang, Y., 2019. DDW 2019 ASGE Program and Abstracts, Gastrointestinal Endoscopy.

Zhao, L., Xiong, Q., Stary, C.M., Mahgoub, O.K., Ye, Y., Gu, L., Xiong, X., Zhu, S., 2018. Bidirectional gut-brain-microbiota axis as a potential link between inflammatory bowel disease and ischemic stroke. J. Neuroinflammation 15, 339. https://doi.org/10.1186/s12974-018-1382-3

Zhao, Q., Elson, C.O., 2018. Adaptive immune education by gut microbiota antigens. Immunology 154, 28–37. https://doi.org/10.1111/imm.12896

Zhao, Y., Cong, L., Lukiw, W.J., 2017. Lipopolysaccharide (LPS) Accumulates in Neocortical Neurons of Alzheimer's Disease (AD) Brain and Impairs Transcription in Human

Neuronal-Glial Primary Co-cultures. Front. Aging Neurosci. 9, 407. https://doi.org/10.3389/fnagi.2017.00407

Zhou, Y., Smith, D., Leong, B.J., Brännström, K., Almqvist, F., Chapman, M.R., 2012. Promiscuous cross-seeding between bacterial amyloids promotes interspecies biofilms. J. Biol. Chem. 287, 35092–35103. https://doi.org/10.1074/jbc.M112.383737

Zhu, L., Baker, S.S., Gill, C., Liu, W., Alkhouri, R., Baker, R.D., Gill, S.R., 2013. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatol. Baltim. Md 57, 601–609. https://doi.org/10.1002/hep.26093

Zhuang, Z.-Q., Shen, L.-L., Li, W.-W., Fu, X., Zeng, F., Gui, L., Lü, Y., Cai, M., Zhu, C., Tan, Y.-L., Zheng, P., Li, H.-Y., Zhu, J., Zhou, H.-D., Bu, X.-L., Wang, Y.-J., 2018. Gut Microbiota is Altered in Patients with Alzheimer's Disease. J. Alzheimers Dis. JAD 63, 1337–1346. https://doi.org/10.3233/JAD-180176

Ziegler, D.M., 1988. Flavin-containing monooxygenases: catalytic mechanism and substrate specificities. Drug Metab. Rev. 19, 1–32. https://doi.org/10.3109/03602538809049617